DIABETES

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The Glucose Tolerance Test after Cortisone Administration in Obese and Nonobese Men

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Study recently has been concentrated upon the common abnormality, obesity, especially as it is related to chronic diseases of a degenerative nature. For many years an association between obesity and diabetes mellitus has been recognized, though in many respects the relationship is not clear. According to statistics of a large insurance company[1] "relatively, the most striking penalty for overweight is diabetes. The death rate from this disease among men 25 per cent or more overweight has been found eight times as high as among average weight persons; and as compared with underweights, thirteen times as high."

The apparent increased incidence of diabetes in recent years may be related either to changing dietary habits or to better diagnostic methods combined with increased diagnostic efforts of physicians.

There also now exists the concept of a "prediabetic" state,[2] and efforts have been made to detect potentially diabetic individuals from among groups having known increased incidence of the disorder.[3] Also surveys have been conducted to detect unrecognized diabetes among an apparently healthy population.

The state of obesity according to Newburgh[4] is "a condition in which the body contains an abnormally large amount of adipose tissue." Tables[1,5] are available indicating ideal weights of men and women depending on height and body build. In the study to be presented, an individual is considered obese if his weight exceeds the ideal weight range. He is considered nonobese if he falls within his ideal range.

The ability of ACTH and cortisone to produce a temporary diabetic state may become useful diagnostically and can be utilized in the study of disorders of carbohydrate metabolism. By preceding the standard glucose tolerance test with ACTH or cortisone Fajans and Conn[3] found that a diabetic type curve usually will become more abnormal. They have performed the glucose tolerance test before and after cortisone "priming" on apparently normal relatives of persons with known diabetes. Utilizing only the standard test without steroids, 19 per cent of 152 relatives of diabetic patients were found to have unsuspected diabetes. Cortisone "priming" followed by the same glucose tolerance test was then performed on the remaining 81 per cent, all presumedly nondiabetic relatives; 24 per cent of the latter showed a marked loss of carbohydrate tolerance while this occurred in only 3 per cent of controls.

It was felt that application of such a cortisone glucose tolerance test to another group of well individuals known to have increased incidence of diabetes would be an additional approach to the problem of the prediabetic state and to the relationship between corpulence and diabetes. Further, it was hoped that comparison of the response of obese and nonobese individuals in a balanced study would delineate information potentially, though not presently, of diagnostic value. In the study being reported, answers to the following questions were sought: On the average, do nonobese and obese test subjects develop significantly different blood sugar levels when tested by the glucose tolerance test, independent of cortisone "priming"? Does cortisone "priming" increase the blood sugar response independent of the degree of obesity of the test subjects? Does cortisone "priming" affect the nonobese and the obese in the same way?

MATERIALS AND METHODS

The tests were conducted under conditions to be expected in the average clinic or hospital, the purpose being to obtain values which could be duplicated should this type test be applied clinically. Thus rigidly weighed pretest diets and unusual restriction of activity were avoided, though men who ostensibly were uncooperative or who developed even mild infections before the tests were eliminated from the series.

Eighty male inmates of the Federal Penitentiary, Terre Haute, Indiana, were studied. None of these volunteers

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This study was conducted at the U. S. Penitentiary, Terre Haute, Indiana.

From the National Institutes of Health, Bethesda, Maryland.

had a family history or suggestive past history of diabetes, and all were ambulatory and completely well as determined by interview and physical examination. The weights without clothing were recorded immediately before testing. Forty men weighed between 111 and 160 lb. (arithmetic mean of 149 lb.), and forty were obese, weighing between 200 and 255 lb. (arithmetic mean of 214 lb.). Each man considered obese weighed from 11 to 66 lb. over his ideal weight.[1] The nonobese men's ages ranged from twenty to fifty-six years, averaging thirty years; the obese men ranged from twenty to fifty-five, averaging thirty-three years.

Each inmate was required to eat the full institution diet (containing daily over 3,000 calories) during three days preceding the testing. A thirteen-hour overnight fast preceded each test, and the men remained at rest during the test. The Folin-Wu method of blood sugar determination was used, the usual fasting blood level being 80-120 mg. per cent. A test included a fasting blood specimen after which 100 gm. of glucose dissolved in 300 ml. of water were given orally in a single dose. Blood specimens then were withdrawn thirty minutes, sixty minutes, ninety minutes, two hours, three hours, four hours, and five hours after glucose administration. Urine specimens were collected simultaneously.

This standard glucose tolerance test (hereafter abbreviated GTT) was performed on each individual at the beginning of the study. Five to seven days later oral cortisone dosage was given, and the oral GTT was repeated. (Hereafter the cortisone-primed GTT will be abbreviated CGTT.) The cortisone was given in two doses, one at eight and one-half and one at two hours, before the glucose test dose was administered (50 mg. per dose for the nonobese men, 62.5 mg. per dose for the obese, as used by Fajans and Conn).[3]

RESULTS AND COMMENTS

Summarized in table 1 are the data obtained in the two groups of men before and after cortisone. Recorded are the arithmetic mean, the standard deviation (SD), and the range of arithmetic mean ± 2SD for each period of the tests. Figures 1A and 1B graphically compare the values of the GTT and the CGTT in these two groups individually, figure 1C in the combined eighty men. The contours of the graphs are strikingly similar in the groups compared.

Certain tests (twenty-three of the GTT's and only four of the CGTT's) showed "dipping" of the glucose level after the peak level was reached but prior to the two-hour point. This phenomenon has been noted in varying incidence in other reported series of GTT's.[9,12] The frequency with which this dip is detected depends upon the number of interval blood glucose determinations made before the two-hour point; as ordinarily performed clinically, no sample is obtained at the ninety-minute point. Some observers[9,12] have felt that a high

TABLE 1

Glucose tolerance tests before and after cortisone

	Fasting	30 min.	1 hr.	90 min.	2 hr.	3 hr.	4 hr.	5 hr.
Nonobese, before cortisone:								
Arithmetic mean	104	153	142	122	109	101	98	93
Standard deviation	12	21	28	26	22	20	15	12
Mean±2 SD	80-128	110-196	87-197	71-173	65-153	60-142	67-128	70-116
Nonobese, after cortisone:								
Arithmetic mean	110	161	168	156	139	123	115	103
Standard deviation	12	23	33	30	25	19	15	8
Mean±2 SD	87-133	115-207	102-234	96-216	89-189	84-162	85-145	88-118
Obese, before cortisone:								
Arithmetic mean	105	151	148	129	124	115	106	99
Standard deviation	12	19	32	31	31	24	20	12
Mean±2 SD	82-128	113-189	83-213	67-191	63-185	66-164	66-146	75-123
Obese, after cortisone:								
Arithmetic mean	114	161	171	156	136	121	115	105
Standard deviation	18	23	41	44	51	25	19	12
Mean±2 SD	78-150	115-207	89-253	68-244	34-238	71-171	77-153	81-129
Obese (selected*) after cortisone:								
Arithmetic mean	113	159	166	150	127	118	113	104
Standard deviation	15	21	32	29	17	11	10	8
Mean±2 SD	83-144	118-200	106-231	92-208	94-160	95-141	93-133	90-119

*Omitting those obese individuals who displayed a diabetic curve on the routine GTT before cortisone.

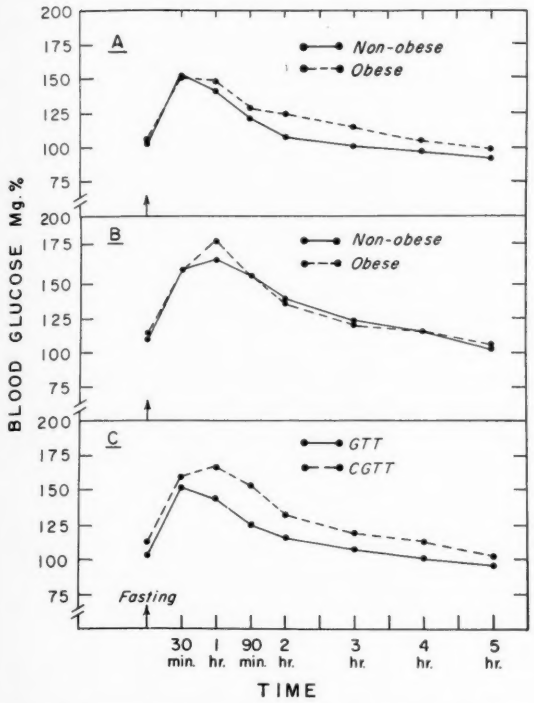

FIG. 1A. Comparison of GTT in nonobese and obese men (mean values).
FIG. 1B. Comparison of CGTT in nonobese and obese men (mean values).
FIG. 1C. Comparison of GTT and CGTT in eighty men (mean values).

two-hour level when occurring in this sequence of events (i.e., a peak blood level, then a drop, and then a second peak at two hours) lacks the significance of a high two-hour level which is on the downward slope of a high or prolongedly elevated curve. Of interest in the present series of tests is the decreased incidence of the dip phenomenon after cortisone priming.

Through a statistical analysis of the data (table 2) for all eighty men it can be concluded that cortisone priming does elevate the blood sugar levels. Table 3 summarizes the average responses at the two-hour period for each group, for each type test. The precortisone average of 117.0 compared with a postcortisone average of 137.8 is significant at the 1 per cent level (table 2, $F = 27.79$ with 1 and 78 degrees of freedom[11]). On the other hand the average of the nonobese group (124.5) compared to the obese group (130.4) is not significantly different. On examining the averages in each quadrant of table 3 it is apparent that the significant total difference between the pre- and postcortisone averages is due mainly

TABLE 2

Statistical analysis of glucose tolerance test data. Consideration of the two-hour blood glucose level.

Source	df*	Sum of Squares	Mean Square	F[11]
Mean	1	2,597,176		
Total	159	198,481		
Obese vs. nonobese	1	1,387	1,387	
Precortisone vs. postcortisone	1	17,368	17,368	27.79†
Weight × cortisone	1	3,303	3,303	5.28‡
Residual	156	176,423		
Individual × cortisone	78	48,720	625	
Individuals within cortisone or noncortisone	78	127,703	1,637	

*df=degrees of freedom[11]
†significant at P=0.01
‡significant at P=0.05

to the difference of 109.5 and 139.4 in the nonobese group (contrasted to the 124.5 and 136.2 of the obese group). It is also apparent on examination of the individual averages in table 3 that in the precortisone column the obese average is much larger than the nonobese average (124.5 vs. 109.5). However, in the postcortisone column the nonobese average of 139.4 is larger than the obese average of 136.2. This reversal seems to indicate that cortisone priming produces a different response in the nonobese group as contrasted to the obese group. This nonuniformity of response is termed interaction. The F-value of 5.28 in table 2 tests whether this interaction is significant, and according to the tabulated F-value with 1 and 78 degrees of freedom, the interaction is significant at the 5 per cent level.

This fact was further investigated by analysis of the individual differences in the blood sugar level at two hours before and after cortisone priming (table 4). A negative sign prefixing the number shows that the postcortisone-priming blood sugar response was less than

TABLE 3

Average blood sugar (two-hour) levels response for pre- and postcortisone priming by obese and nonobese groups

	Precortisone priming GTT	Postcortisone priming GTT	Average
Nonobese	109.5	139.4	124.5
Obese	124.5	136.2	130.4
Average	117.0	137.8	127.4

TABLE 4

Measurement response at two hours; individuals showing a negative difference after cortisone priming

	Case No.	Precortisone priming	Postcortisone priming	Difference Post-minus Pre-
Nonobese				
	3	120	117	− 3
	30	128*	120	− 8
	33	128	120	− 8
	34	136	133	− 3
	38	133	128	− 5
	39	140	124	−16
Obese				
	42	117	109	− 8
	50	120	105	−15
	54	120*	109	−11
	65	136*	133	− 3
	66	161*	128	−33
	69	128	124	− 4
	70	133	117	−16
	72	145	117	−28
	73	128	124	− 4
	76	140	113	−27
	77	148	124	−24
	78	175*	140	−35
	79	188*	153	−35

*Curve shows "dip phenomenon."

the blood sugar response before cortisone. In the nonobese group there are 15 per cent (six out of forty) negative differences. In the obese group there are 32.5 per cent (thirteen out of forty) negative differences. The two proportions of negative differences are almost significantly different. However, if those individuals exhibiting the dip phenomenon are eliminated from table 4 there are only five nonobese (12 per cent) and eight obese (20 per cent) with negative differences, then certainly not significant. Therefore, one finds no difference in response to cortisone priming between the nonobese and the obese as groups. The apparent difference found if the dip phenomenon is not considered and only the two-hour level is studied points out the importance of making frequent sugar determinations before the two-hour point when performing the GTT.

Further analysis of these individuals exhibiting a negative postcortisone difference (table 4) indicates that in 100 per cent of the nonobese negatives (six of six) and in 77 per cent (ten of thirteen) of the obese there was a two-hour level higher than average on the standard GTT. The mean two-hour level for these six nonobese was 133, contrasted to the total group mean of 109. For the thirteen obese a mean of 141 contrasts to the total group mean of 124.

It is of interest that among these eighty men one nonobese man (2.5 per cent) and four obese men (10.0 per cent) had diabetic type standard GTT (using as criteria of abnormal a ninety-minute level of 160 or over and a two-hour level of 140 or over).[3,10]

DISCUSSION

The occurrence of disturbed carbohydrate metabolism resembling diabetes mellitus in some middle-aged obese individuals can frequently be controlled by weight reduction. As interpreted by Newburgh this hyperglycemia does not represent true diabetes.[6] Past studies[7] have suggested that the impaired glucose tolerance in obese females is related to the duration of the obesity, coming on only after many years of obesity. The corpulent men in the present study were of mean age thirty-three; the possibility exists that an older group of obese individuals would demonstrate a different response to cortisone priming.

When preceded by cortisone the GTT was thought to indicate marked loss of glucose tolerance in 24 per cent of apparently normal relatives of diabetics studied by Fajans and Conn. This suggests that the CGTT is a situation to which abnormal responses can be expected if individuals from a group having an increased tendency to diabetes mellitus are tested. In the present study evidence has been obtained that the obese as a group (average age thirty-three years) do not respond differently from the nonobese as a group when submitted to the CGTT. The results, therefore, are in agreement with the idea[8] that the "diabetes" of middle-aged obese persons may be a different type of carbohydrate intolerance from that seen in true diabetes mellitus.

Analysis of these data, however, shows some nonuniformity of response (termed "interaction") between the nonobese and the obese as groups when both the GTT and the CGTT are studied comparatively. Considering the two-hour glucose level, the obese show significantly less rise after cortisone priming than do the nonobese (table 3). Yet, the two-hour average of the two groups is practically the same (139.4 mg. per cent and 136.2 mg. per cent). Further, more of the obese individuals (thirteen) than of the nonobese (six) actually show a decrease in their two-hour level after cortisone (table 4). Three obese individuals who demonstrated diabetic-type routine GTT's showed a decrease in the two-hour level after cortisone priming. Though the meaning of this interaction is speculative, it suggests that an existing difference in carbohydrate tolerance between the obese and nonobese as groups is eliminated by cortisone administration.

In these eighty prisoners the blood sugar levels in general seemed slightly higher than in other large series of glucose tolerance tests.[9,10] Also, of forty obese men four demonstrated an abnormal routine GTT, a higher proportion than reported by other authors. Among several factors to be considered, perhaps, would be the emotionally stressful situation of incarceration, the somewhat unique psychologic status of the group as a whole, and the diminished physical activity of such a life.

No effort was made in this study to determine what a "diagnostic" CGTT is, since the "cut off points" (defined below) both as to height of the blood sugar level and as to duration of a certain level have not been determined. No large group of diabetics has been subjected to this test. Fajans and Conn in considering the two-hour sugar level used three standard deviations from the mean as representing a high degree of significance in the CGTT. If such a level were applied to the present group one nonobese individual and one obese individual could be considered to exhibit marked loss of glucose tolerance when primed with cortisone before testing. However, this obese one earlier had demonstrated definite abnormality on the routine GTT.

The term "cut off point" refers to the point or the range above which all abnormal (or diabetic, in this case) individuals will be found, and below which all normals will fall. A "cut off point" may not be sharp, but may be a wide range in which some normals and in which some abnormals will be found. In such a test the relative values and dangers resulting from a "false positive" or a "false negative" test must be weighed. This reasoning is the basis for avoiding the terms "diagnostic test" or "positive test" in such a study as the present one, until many diabetics as well as nondiabetics have been studied to determine where the "cut off point" or "cut off range" lies. Long term follow-up study of individuals exhibiting apparently abnormal glucose tolerance on CGTT will also be necessary. Till then, no conclusions should be drawn regarding the diabetic or nondiabetic propensities either of a selected group of individuals or of a given individual.

The tolerance tests were extended to the five-hour period as a further means of elucidating the glucose tolerance. The values and the range exhibited at four and five hours in these eighty men also represent the values to be expected normally when such prolongation of the standard GTT is applied in clinical practice.

SUMMARY

Forty nonobese and forty obese healthy individuals with no family history of diabetes were subjected to a standard glucose tolerance test. Subsequently this was repeated except that oral cortisone was given during the night preceding the test.

Cortisone administration produced a significant decrease in carbohydrate tolerance in the eighty men as a group. The average two-hour blood glucose level rose from 117.0 mg. per cent before cortisone to 137.8 per cent after cortisone priming.

No significant difference existed between the two groups as to the two-hour response on the standard glucose tolerance test. Likewise, there was no difference after cortisone priming; both the nonobese and the obese groups responded in the same fashion. However, a statistically significant "interaction," or nonuniformity of response, existed between the two groups when the responses to the precortisone glucose tolerance tests were compared to those of the postcortisone glucose tolerance tests. This interaction seemed in part due to a difference in the two-hour level reached by the two groups on the precortisone glucose tolerance test. It suggested that cortisone produced homogeneity in the two groups in their response to a carbohydrate load.

SUMMARIO IN INTERLINGUA

Le Test Del Tolerantia Pro Glucosa Post Administrationes De Cortisona In Masculos Obese E Non-Obese

Quaranta obese e quaranta non-obese individuos normal, sin historia familial de diabete, esseva subjicite al test standard de tolerantia pro glucosa. Le manovra esseva repetite subsequentemente con le sol differentia que cortisona oral esseva administrate durante le nocte ante le test.

Le administration de cortisona produceva un reduction significative in le tolerantia pro hydrato de carbon in le gruppo integre del octanta subjectos. Le valor medie del nivello de glucosa in le sanguine post duo horas montava ab 117,0 mg pro cento ante cortisona a 137,8 mg pro cento post cortisona.

Nulle differentia significative existeva inter le duo gruppos quanto a lor responsas, al periodo de duo horas, al test standard de tolerantia pro glucosa. Similemente, nulle differentia se manifestava post le administration de cortisona. Le gruppo obese e le gruppo non-obese reageva in le mesme maniera. Tamen, un "interaction," i.e. un non-uniformitate del responsa, de un grado de signification statistic, existeva inter le duo gruppos quando le responsas in le tests de tolerantia pro glucosa ante le uso de cortisona esseva comparate con illos in le tests de tolerantia pro glucosa post le uso de cortisona. Il pareva que iste interaction esseva debite in parte al differentia del nivellos attingite per le duo gruppos al periodo de

duo horas in le test de tolerantia pro glucosa ante le uso de cortisona. Es suggerite que cortisona produceva homogeneitate del duo gruppos in lor responsas al carga de hydrato de carbon.

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Essential Fatty Acids and Biological Functions

Essential fatty acids are required for maintenance of a variety of biological functions. Deficiency results in diminished growth and structural changes in many tissues. The histological changes in the skin of deficient animals are accompanied by markedly increased water permeability. Kidney structure may become so deranged that hematuria results. Essential fatty acid deficiency leads to impaired reproduction. Pregnant female rats fed diets deficient in essential fatty acids do not deliver normal offspring, and degeneration of germinal epithelium has been observed in testes of male rats fed a diet which severely depleted them of essential fatty acids. The lipids of the gonads contain an unusually high proportion of polyunsaturated acids, suggesting the importance of these substances in reproductive function. The polyunsaturated acids are found in higher concentration in tissue structural lipids than in depot fats, and deficiency symptoms are most easily induced during physiological conditions when rapid cell division occurs.

Recently the essential fatty acids have been implicated in the problem of atherosclerosis. Although it is not known if hypercholesterolemia is a cause of atherosclerosis and/or myocardial infarction, it is considered to be an undesirable indicator of potential disease. The inclusion of high levels of saturated fat in the diets of animals and humans induces hypercholesterolemia, whereas diets containing a high level of unsaturated oils containing large proportions of essential fatty acids depress the level of plasma cholesterol (*Lancet II*, 943, 1957). The clotting time of blood seems to be prolonged and the fibrinolysin activity of blood is increased by the ingestion of fats rich in essential fatty acids, whereas diets rich in saturated fatty acids (hard fats) shorten clotting time and decrease the fibrinolysin activity. Therefore dietary essential fatty acids or polyunsaturated fatty acids exert three biological effects which tend to delay or prevent atheroma according to current concepts.

Ralph T. Holman, Ph.D., in *Nutrition Reviews*, Vol. 16, No. 2, p. 34.

Direct Effects of Tolbutamide and Insulin on Peripheral Glucose Uptake

A Comparative Study in Man

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INTRODUCTION

The mechanism and site of the hypoglycemic action of the sulfonylurea drugs have been the subject of much research and speculation.[1,2] It has been postulated that the blood glucose-lowering effect of these compounds is mediated through endogenous insulin, perhaps by enhancement of insulin output from the pancreas.[3] Several investigators have attempted to test the validity of this hypothesis by comparing the effects of the sulfonylureas and exogenous insulin on various parameters of glucose metabolism. The basis for this approach has been the assumption that, if the action of the sulfonylureas was mediated through insulin, the metabolic effects of the two substances would be similar. The peripheral arterial-venous blood glucose concentration difference is one parameter which has been studied. While it is generally agreed that insulin increases this difference in both man and the dog,[4-7] studies of the influence of the sulfonylureas on peripheral glucose uptake have yielded apparently inconsistent results. Goetz and his co-workers[6] reported that both the oral and intravenous administration of tolbutamide increased the peripheral arterial-venous glucose difference in man and a similar effect of the intravenously administered drug was observed in the dog.[7] Others have failed to demonstrate such an effect when the drug was given to human subjects by either the intravenous[8,9] or oral[10] route; oral administration of tolbutamide did not increase the peripheral arterial-venous glucose difference in the dog.[11] In the studies cited, a direct action of tolbutamide on the peripheral tissues was not differentiated from an indirect effect mediated through another substance, such as endogenous insulin. In the present study the direct effects of tolbutamide and exogenous insulin on peripheral glucose uptake were compared by injecting small doses of these drugs into the brachial artery and determining the arterial-venous glucose concentration difference in the forearm. Recant and Fisher[9] have reported the preliminary results of similar experiments.

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METHODS

The subjects for these studies were eight nondiabetic male hospital patients. Six were tested twice, once each with insulin and tolbutamide, to compare the effects of the two drugs in the same subject. Each test was performed with the patient resting in bed following an overnight fast. Blood samples were obtained simultaneously through indwelling needles in the brachial artery and a major antecubital vein of the same extremity. During a preliminary control period of thirteen to twenty-eight minutes, three pairs of arterial and venous blood samples were obtained. Glucagon-free crystalline insulin* (0.01 unit per kg. of body weight) or sodium tolbutamide† (0.2 or 0.4 gm., irrespective of body weight, as a 5 per cent solution in distilled water) was then administered by injection into the indwelling needle in the brachial artery during a two-minute period. Arterial and venous blood samples were obtained simultaneously at five-minute intervals for the next half hour and at ten-minute intervals for the second half hour. The tests were repeated in the same subjects two to forty-nine days later; care was taken to sample blood from the same sites used in the initial test and an identical experimental procedure was followed except for the use of the other one of the two drugs under comparison. In subjects C. F. and J.W. the insulin test preceded that with tolbutamide; in the other four subjects the order was reversed. The seventh and eighth patients served as control subjects and were studied in the manner described above except that 10 ml. of 0.9 per cent sodium chloride solution was injected instead of insulin or tolbutamide. The blood glucose content was determined in duplicate by the titrimetric method of

* Supplied by Dr. W. R. Kirtley of Eli Lilly and Company.
† Supplied by Dr. C. J. O'Donovan of The Upjohn Company.

Somogyi;[22] the results were accurate to within 2 mg. per 100 ml. at the blood glucose levels encountered. The plasma tolbutamide concentration was determined in some of the samples by the method of Miller et al.[23] The statistical significance of changes in the average arterial-venous blood glucose concentration difference was assessed by the "t" test of Fisher.

RESULTS

The results are shown in table 1 and figure 1.

The intra-arterial injection of insulin lowered the arterial blood glucose concentration in all six subjects. The maximum reduction ranged from 2 to 16 mg. per 100 ml. with an average of 9 mg. per 100 ml. The maximum decrease in blood glucose occurred at fifteen to twenty-five minutes after insulin injection. In five of the six patients an increase in the arterial-venous blood glucose concentration difference in the injected forearm was noted within five or ten minutes after insulin administration and persisted until at least thirty minutes after administration. The average control difference ± one standard deviation was 0.1 ± 1.4 mg. per 100 ml. and the average of the values obtained at five-minute intervals for the first thirty minutes after insulin administration was 6.4 ± 3.4 mg. per 100 ml.; this increase is statistically significant ($p<0.01$).

In the same six subjects, the intra-arterial injection of tolbutamide lowered the arterial blood glucose concentration by 6 to 29 mg. per 100 ml., the average being 17 mg. per 100 ml. The maximum decrease occurred twenty to fifty minutes after tolbutamide administration. In four patients the maximum glucose fall exceeded that produced by insulin. No explanation could be found for the higher average initial arterial blood glucose concentration before tolbutamide administration as compared to the initial value before insulin injection. No consistent increase in the arterial-venous blood glucose concentration difference was observed in any of the six subjects during the first thirty minutes after tolbutamide injection. Rather, the average arterial-venous glucose difference declined from a control value ± one standard deviation of 3.0 ± 1.8 mg. per 100 ml. to an average of 1.3 ± 1.0 mg. per 100 ml. for the values obtained at five-minute intervals during the first thirty minutes after tolbutamide administration ($0.05<p<0.1$). The tolbutamide concentration was determined in nine pairs of samples obtained simultaneously from the brachial artery and antecubital vein of the injected extremity of three of the subjects at five to thirty minutes after injection of the drug. The plasma tolbutamide concentration was consistently higher in the venous blood from the injected extremity than in the arterial blood. The average concentration at five minutes was 2.8 mg. per 100 ml. in the arterial sample and 11.3 per 100 ml. in the venous sample; the corresponding values at thirty minutes were 2.9 and 4.0 mg. per 100 ml. Three patients complained of a sensa-

TABLE 1

Arterial blood glucose concentrations (A) and arterial-venous blood glucose concentration differences (A-V) in the forearm before and after the injection of insulin, sodium tolbutamide, or sodium chloride into the brachial artery*

Subject	Dose	Blood glucose concentration (mg./100 ml.) Minutes after injection																			
		0†		5		10		15		20		25		**30**		40		50		60	
		A	A-V	A	A-V	A	A-V	A	A-V	A	A-V	A	A-V	A	A-V	A	A-V	A	A-V	A	A-V
	Units	Insulin																			
P. G.	0.85	91	1.0	93	5	87	5	88	8	88	10	84	6	85	6	84	0	85	3	83	—1
W. K.	0.70	81	1.3	80	9	70	5	66	12	65	10	66	13	70	12	71	7	77	5		
W. C.	0.54	66	—1.7	64	—2	66	6	56	1	59	6	54	3	60	11	63	11	61	5	62	5
C. F.	0.60	70	—1.3	70	—1	71	6	68	6	71	6	73	2	76	5	74	3	81	7	83	6
M. P.	0.82	78	—0.3	75	0	73	13	70	13	68	13	69	11	71	14	73	7	73	5	69	6
J. W.	0.60	79	1.7	74	0	76	5	72	3	74	2	78	2	77	3	79	4	74	—1	75	5
Mean		78	0.1	76	1.8	74	6.7	70	7.2	71	7.8	71	6.2	73	8.5	74	5.3	75	4.0	74	4.2
	Grams	Tolbutamide																			
P. G.	0.2	104	3.3	103	4	104	4	102	2	98	—1	101	5	101	2	100	3	99	1	98	3
W. K.	0.4	108	2.3	101	1	105	3	97	2	93	—1	93	0	88	—1	92	9	95	7	94	2
W. C.	0.4	73	5.7	67	0	64	—1	62	3	62	0	57	—1	58	0	59	0	59	—1	61	—1
C. F.	0.4	90	2.3	84	2	83	3	75	0	68	1	71	4	70	0	70	0	74	1	75	3
M. P.	0.4	93	4.0	91	5	83	0	78	—2	77	3	73	—1	78	7	73	3	64	—7	64	—1
J. W.	0.4	76	0.3	72	5	70	0	66	0	64	1	63	—3	66	0	62	—2			68	0
Mean		91	3.0	86	2.8	85	1.5	80	0.8	77	0.5	76	0.7	77	1.3	76	2.2	78	0.2	77	1.0
	Ml.	0.9% Sodium Chloride																			
J. M.	10	83	2.3	86	6	80	1	81	0	85	3	79	—1	84	3	84	3	83	5	82	5
R. B.	10	73	0.7	70	0	70	5	71	0	70	0	70	0	68	0	71	3	70	3	70	3

* Unless indicated otherwise, A-V differences were positive.
† Average of three samples.

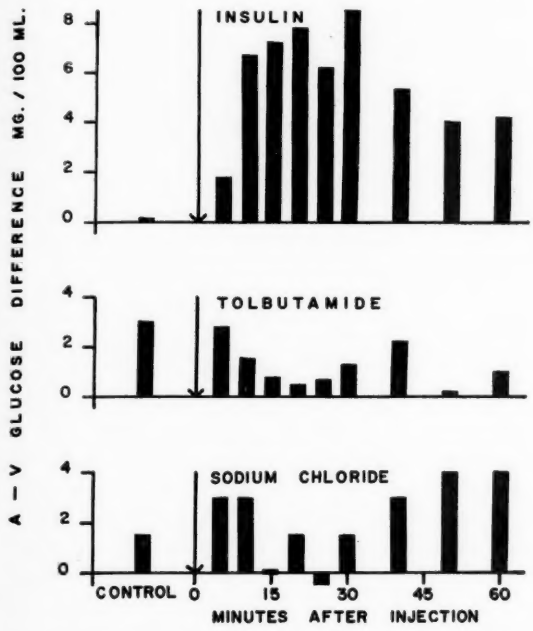

FIG. 1. Average arterial-venous blood glucose concentration differences in the forearm before and after the injection of insulin, tolbutamide, or sodium chloride into the brachial artery. The results with insulin and tolbutamide were obtained in the same six subjects. The tests with sodium chloride were performed in two other subjects. The control bars represent the average of three observations in each subject.

tion of warmth in the hand while tolbutamide was being injected, but no objective changes were observed.

In the seventh and eighth subjects, the intra-arterial injection of a sodium chloride solution produced no consistent changes in the arterial blood glucose concentration or the arterial-venous glucose concentration difference. In these two subjects, the average arterial-venous blood glucose concentration differences were 2.3 and 0.7 mg. per 100 ml. in the control period and 2.0 and 0.8 mg. per 100 ml., respectively, during the first thirty minutes after saline injection.

DISCUSSION

These results fail to demonstrate a direct stimulatory effect of tolbutamide on glucose uptake in the forearm in contrast to the positive effect of insulin. Recant and Fisher[9] obtained similar results in preliminary experiments. The findings are compatible with the failure of tolbutamide and carbutamide to enhance glucose uptake or glycogen deposition in the isolated rat diaphragm.[9,14,15,16] They also accord with the lack of effect of tolbutamide on the level of circulating blood glucose in the eviscerated animal.[17-21]

The data suggest that a decrease in the peripheral arterial-venous blood glucose concentration difference may have followed tolbutamide administration; a similar trend was noted by Anderson et al.[11] and Purnell et al.[8] However, this decrease may be due to the decline in the arterial blood glucose concentration[22] rather than to a direct inhibitory effect of tolbutamide itself.

Changes in the arterial-venous concentration difference of glucose reflect accurately changes in glucose uptake in an extremity only if the rate of blood flow through the extremity remains constant. Therefore, the above conclusions regarding glucose uptake are valid only if the intra-arterial injection of insulin and tolbutamide did not significantly alter the rate of peripheral blood flow. After insulin administration, an increase in the rate of blood flow in the hand has been observed in normal subjects when the venous blood glucose concentration was reduced to approximately one-third of the initial fasting level;[23] in schizophrenic patients the blood flow in the extremities was elevated when the venous blood glucose concentration fell to below 15 mg. per 100 ml.;[24] a reduction of capillary blood glucose concentration to levels between 28 and 49 mg. per 100 ml. was associated with an increased rate of blood flow in the hand and forearm of bilaterally adrenalectomized subjects who were given insulin.[25] The rate of blood flow in the forearm was increased in two subjects whose capillary blood glucose concentrations were lowered to 55 and 56 mg. per 100 ml. by the oral administration of tolbutamide.[26] Since the minimum venous blood glucose concentrations attained after tolbutamide administration in the six subjects of the current study ranged from 58 to 95 mg. per 100 ml. (average 72 mg. per 100 ml.), it is improbable that hypoglycemia altered the rate of blood flow. We have found no reports of measurements of the peripheral blood flow after the intra-arterial administration of insulin or tolbutamide.

The failure to demonstrate a direct peripheral effect of tolbutamide in the present study is probably not due to an inadequate dose of the drug: The arterial blood glucose concentration fell in the presence of low levels of the drug in the systemic blood, while no effect was observed in the injected forearm where the concentration of tolbutamide was greater. The persistence of higher tolbutamide levels in the venous blood from the injected forearm than in the arterial blood suggests that the level of the drug in the extracellular fluid of the forearm exceeded that in the systemic circulation for at least thirty minutes after injection.

The decrease in arterial blood glucose concentration

in the absence of an increase in the peripheral arterial-venous glucose concentration difference indicates that, under the conditions of these experiments, tolbutamide was exerting its blood glucose-lowering effect at a non-peripheral site. Previous studies have shown that the splanchnic system is one nonperipheral site which may be involved in the action of tolbutamide.[8,9,11,27–30]

The present results do not refute the hypothesis that the blood glucose-lowering effect of tolbutamide is mediated by endogenous insulin acting at a nonperipheral site. Neither do they exclude the possibility that under other conditions the peripheral tissue might be involved in the hypoglycemic action of tolbutamide. Different investigators have used different doses of tolbutamide given by various routes to human subjects and animals under a variety of experimental conditions.[6–11] The discrepancies in the results obtained may thus be more apparent than real.

SUMMARY

The direct effects of tolbutamide and exogenous insulin on peripheral glucose uptake were compared by injecting small doses of these drugs into the brachial artery and determining the arterial-venous blood glucose concentration difference in the forearm. Each one of six nondiabetic patients was tested twice, once with insulin and on another occasion with tolbutamide. The injection of insulin (0.01 unit per kg. of body weight) into the brachial artery produced a prompt and significant increase in the arterial-venous glucose difference in the forearm in five of the six subjects; the average difference rose from 0.1 ± 1.4 mg. per 100 ml. in the control period to 6.4 ± 3.4 mg. per 100 ml. during the first thirty minutes after insulin administration. In contrast, tolbutamide (0.2 or 0.4 gm.) did not produce a consistent increase in the arterial-venous glucose difference in any of the six subjects; the average control difference was 3.0 ± 1.8 mg. per 100 ml. as compared to 1.3 ± 1.0 mg. per 100 ml. after tolbutamide. The fall in the arterial blood glucose concentration after tolbutamide in the apparent absence of an increase in the rate of peripheral glucose uptake suggests that this drug has a nonperipheral site of action under these experimental conditions.

SUMMARIO IN INTERLINGUA

Un Comparation Del Effects Directe De Tolbutamido E De Insulina Super Le Acceptation Peripheric De Glucosa In Humanos

Le effectos directe de tolbutamido e de insulina exogene super le acceptation peripheric de glucosa esseva comparate per injicer micre doses del duo drogas in le arteria brachial e determinar le differentia del concentration arterio-venose de glucosa del sanguine in le antebracio. Sex patientes non-diabetic individual esseva testate duo vices, con insulina e con tolbutamido. Le injection de insulina (0,01 unitates per kg de peso corporee) a in le arteria brachial produceva un prompte e significative augmento del differentia inter le concentrationes arterial e venose de glucosa in le antebracio in 5 del 6 subjectos. Le differentia medie montava ab 0,1 ± 1,4 mg per 100 ml durante le periodo de controlo a 6,4 ± 3,4 mg per 100 ml durante le prime 30 minutas post le administration de insulina. Del altere latere, tolbutamido (0,2 o 0,4 g) non produceva uniformemente un augmento del differentia arterio-venose de glucosa in ulle del 6 subjectos. Durante le periodo de controlo, le differentia medie esseva 3,0 ± 1,8 mg per 100 ml, comparate con 1,3 ± 1,0 mg per 100 ml post le administration de tolbutamido. Le reduction del concentration arterial de glucosa del sanguine post le administration de tolbutamido in le absentia apparente de un augmento del acceptation peripheric de glucosa suggere que iste droga ha un sito non-peripheric de action sub le conditiones experimental hic describite.

ACKNOWLEDGMENTS

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Claude Bernard and the Discovery of Glycogen

During the first century of recognition glycogen has passed from a starch-like material of unknown constitution, the immediate precursor of the sugar secreted by the liver, to a substance whose molecule can be enzymically dissected, much as Claude Bernard dissected an animal. Already this power to effect such molecular analysis of glycogen by means of enzymes has differentiated glycogen-storage disease into a number of different types, and has revealed that the peripheral part of the glycogen molecule can undergo metabolic change independently of the central part. What light these new observations will throw on medicine will become clear early in the second century of glycogen. I believe that we can confidently assume that Claude Bernard would have given his interested approval to the many investigations into the structure and biosynthesis of glycogen which have taken place during the last twenty-five years of the first century of this substance.

From the article by F. G. Young, D.Sc., Ph.D., F.R.S., in *British Medical Journal*, June 22, 1957, pages 1431-37.

The Anti-insulin Effect of Epinephrine

Its Significance for the Determination of Serum Insulin by the Rat Diaphragm Method

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INTRODUCTION

Methods for calculating plasma insulin-like activity from the glucose consumption of the rat diaphragm have been described by Groen, Kamminga, Willebrands and Blickman,[1] Willebrands and Groen,[2,3] Vallance-Owen and Hurlock,[4] and Randle.[5] Two types of variations have been encountered that cannot be adequately controlled: (1) There are variations between test animals that are often quite large, and (2) there is sometimes a discrepancy between the serum insulin values and the clinical findings.[2,3] Furthermore, different authors, using substantially the same method, find different values for serum insulin-like activity in normal humans. Willebrands, v. d. Geld and Groen[6] showed that this might in part be due to the different dilutions used in the determination. These authors found, using undiluted serum as incubation medium for the diaphragm, that the serum insulin-like activities were considerably less than those found with serum diluted five to ten times with buffer. As a possible explanation of these observations it was suggested that serum might contain an inhibiting substance, the effect of which diminishes more rapidly on dilution than that of the serum insulin.

Theoretically, epinephrine might complicate the method of assay by its presence either in the diaphragm or in the serum. Epinephrine has been known to have a hyperglycemic action since the work of Cannon.[7] This effect has been ascribed to an increased release of glucose by the liver[8] and decreased utilization of glucose by the muscles. Walaas and Walaas[9] noted that epinephrine caused a decrease in the glucose consumption of the rat diaphragm from 2.8 to 1.9 mg./gm./hr., attended by a reduction in the muscle glycogen and an increase in lactic acid production. Riesser[10] showed that the effect of insulin in producing an increase in muscle glycogen could be completely blocked by epinephrine in the media. Sutherland and Cori[11] showed that epinephrine had an effect on phosphorylase such that the inactive form was converted to the active form.

That epinephrine exerts an effect on the carbohydrate metabolism of the diaphragm seems to be established, but whether this is a significant factor in its use in the assay of small quantities of insulin has not been established. The concentration of adrenalin in the media in the experiments of Walaas and Walaas[9] was 1.0 gamma/ml., while Riesser[10] used concentrations of adrenalin in the range of 5-10 gammas per ml. In the literature some disagreement exists as to the physiological level of epinephrine in the plasma. Weil-Malherbe and Bone[12] described pressor amine levels of 0.005 ($10^{-2.3}$) gamma per ml., while de Valk and Price,[13] using other methods of determination, found the average level of about 0.001 gamma per ml. or less. Thus from the cited work on the effect of epinephrine on the carbohydrate metabolism of the rat diaphragm it cannot be said that this effect is important at physiological levels, since epinephrine concentrations used were 200-10,000 times estimated physiological values. For this reason it seemed important to study how various concentrations of epinephrine and of norepinephrine vary the effect of insulin on the glucose consumption of the diaphragm, in order to arrive at the values for the minimum effective concentrations. Furthermore the influence of added epinephrine on the insulin-like activity of plasma had to be studied.

METHODS

Rat hemidiaphragms were prepared and placed in flasks according to the method for insulin assay described previously.[6] The insulin concentration in the flasks was adjusted to 0.5 milliunit per ml. Just prior to the incubation one flask of each was made up to the desired concentration of epinephrine or norepinephrine. The epinephrine and norepinephrine used were commercially available, synthetic preparations. The epinephrine base was

From the Second Medical Service of the Wilhelmina-Gasthuis, Amsterdam, the Netherlands.

dissolved in a minimum 0.001 HCl and diluted with buffer to the desired concentration. Norepinephrine was available as the bitartrate.

The media were adjusted to *p*H 7.4 and the flasks were shaken at 37° C. for ninety minutes. The glucose concentration of the media was determined by the method of Hagedorn et al.[14] The apparent insulin concentration in the flask containing insulin plus the pressor amine was calculated from the observed glucose uptake as previously described;[6] the per cent depression of the initial insulin activity was then calculated. In the experiments involving serum, the serum, diluted ten times with buffer, was substituted for the buffer solution as the media. The glucose concentration in the media was always adjusted to 150±5 mg. per cent. In experiments where radioactive insulin was used, the diaphragms, after incubation, were washed twice with 25 ml. of buffer for ten minutes each and placed in 1.0 ml. of 15 per cent NaOH in the boiling water bath until dissolved. The volume was then adjusted to 2.0 ml. with water; 1 ml. was next placed in a glass dish and evaporated to dryness, after which the radioactivity was assayed in the end window Geiger counter.

RESULTS

Epinephrine: The addition of epinephrine to the medium in the absence of added insulin produced only a slight effect on the glucose consumption in concentrations from 0.85 gammas/ml. to 15 gammas/ml. A striking effect (figure 1) on the glucose consumption was noted when epinephrine was added to the media containing insulin in a concentration of 5×10^{-4} units/ml.; the expected glucose consumption was suppressed in varying degrees dependent upon the epinephrine concentration. Complete inhibition of insulin effect was noted at concentrations of 10^{-2} gammas/ml. of epinephrine or more. A logarithmic plot of depression at lower concentrations of adrenalin revealed that there was still significant inhibitory effect at concentrations as low as 10^{-4} gammas/ml. of epinephrine.

Norepinephrine: A slight but significant depressing effect was produced on the basal glucose consumption in the absence of added insulin by norepinephrine in concentrations of 1.2 and 12 gammas/ml. Again (figure 1) a most striking effect was noted when insulin was present in the medium in a concentration of 5×10^{-4} units/ml. Here an inhibition of insulin effect was complete at concentrations of norepinephrine of 1 gamma/ml., while significant depression was still noted at concentrations as low as 5×10^{-2} gammas per ml. (figure 1). The curve for norepinephrine inhibition is similar in form to that for epinephrine inhibition, but shifted toward the higher concentration range so that about 100 times as much norepinephrine is required to give the same depressing effect as epinephrine.

Effect of epinephrine and norepinephrine on serum insulin activity: Upon addition of varying concentrations of epinephrine to serum, a suppression of the insulin activity of the serum, diluted ten times, was noted. Figure 2 shows the location of points obtained in this way; the curve approximately fits the concentration-action curve obtained with pure solutions of insulin and epin-

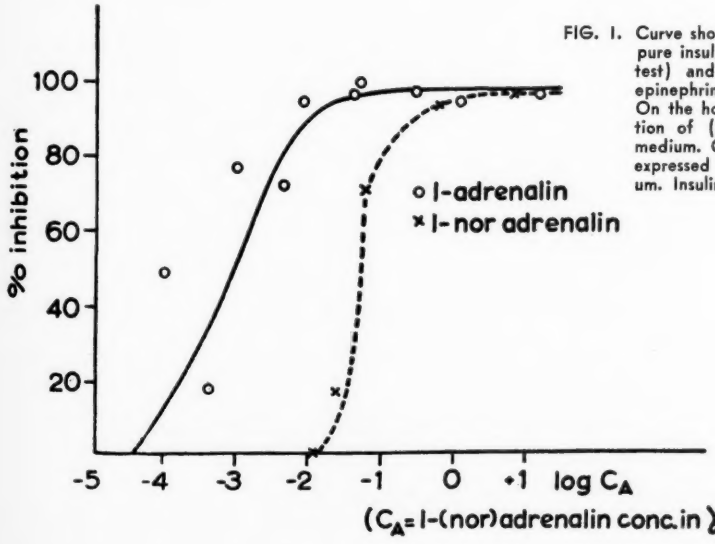

FIG. 1. Curve showing relation between inhibition of activity of pure insulin (as measured in the isolated rat diaphragm test) and the concentration of epinephrine or norepinephrine in the medium.
On the horizontal, on a logarithmical scale: concentration of (nor-)epinephrine in μgm./ml. of incubation medium. On the ordinate: inhibition of insulin activity, expressed as percentages of insulin added to the medium. Insulin concentration in all media 0.5 milliunit/ml.

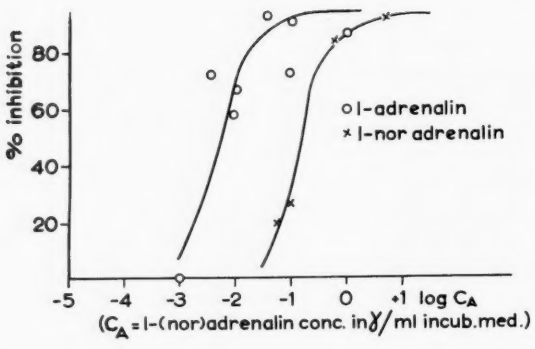

FIG. 2. Curve showing relation between inhibition of insulin activity of ten-times-diluted serum (as measured in the isolated rat diaphragm test) and the concentration of epinephrine or norepinephrine in the medium.
On the horizontal, on a logarithmical scale: Concentration of (nor-)epinephrine in μgm./ml. of incubation medium. On the ordinate: inhibition of insulin activity, expressed as percentages of insulin activity added to the medium.

ephrine. It should be noted that the serum tested showed in most cases a low insulin activity.

Using a serum with higher insulin activity (2.8×10^{-3} units/ml.) the depression produced by varying amounts of norepinephrine fit well with the curve obtained for pure solutions of norepinephrine and insulin.

Effect of sympathetic blocking agents on the epinephrine effect: Komrad and Low[15] have reported the blocking of epinephrine-induced hyperglycemia by the use of various blocking agents. How these substances vary epinephrine's effect on the rat diaphragm was studied by including the blocking agent in the media. The results are shown in table 1. No significant reversal of epinephrine's inhibition of insulin was noted. In higher concentrations (above 10 gammas per ml.) a significant reduction in the insulin-caused augmentation of glucose consumption was noted in the case of ergonovine maleate and 1-phenyl-2-N-methyl-1-benzylaminoethyl . HCl.

Effect of epinephrine on the insulin binding of the diaphragm: Binding of labeled insulin to the diaphragm has been reported by Stadie, Haugaard and Vaughan.[16]

TABLE 1

Effect of sympatholytic and adrenolytic substances on the adrenalin inhibition of the effect of insulin (0.5 U/ml.) on the glucose consumption of the rat diaphragm

Test substance	Epinephrine μgm./ml.	Difference* in glucose utilization mg.$\times 10^{-2} \pm$SEM†	n	P
Ergonovine maleate‡ 10.0	—	—0.8 ± 2.5	5	>0.05
10.0	0.1	3.8 ± 3.3	5	0.30
10.0	—	3.4 ± 4.6	5	>0.10
10.0	0.5	2.8 ± 2.1	5	>0.10
90.0	—	—13.2 ± 1.8	5	<0.01
90.0	0.5	—3.4 ± 2.0	5	>0.10
Ethyl-β-chloroethyl-β-(o-benzyl) phenoxy-ethylamine-HCl‡ 10.0	—	—6.2 ± 4.0	5	>0.10
10.0	0.5	0.6 ± 2.2	5	>0.10
1-phenyl-2N-methyl-benzylamino ethyl-HCl‡ 10.0	—	—14.0 ± 7.9	5	>0.10
10.0	0.5	—5.6 ± 2.0	5	0.05
1.0	0.5	—4.4 ± 2.1	5	>0.10
Dibenzyline§ 10.0	—	—6.0 ± 4.2	5	>0.10
10.0	0.5	—3.4 ± 3.0	5	>0.10
1.0	0.5	—2.2 ± 2.5	5	>0.10
Dibenamine§ 10.0	—	0.4 ± 3.3	5	>0.10
10.0	0.5	—4.2 ± 2.0	5	>0.10
Dihydro ergocornine‖ 10.0	—	—4.2 ± 3.7	5	0.30
10.0	0.5	+0.4 ± 0.5	5	0.40

*Difference in glucose utilization in flask with and without substance to be tested.
†Standard error of mean of the correlated differences.
‡Supplied through the courtesy of the Lilly Research Laboratories, Indianapolis, Indiana.
§Supplied through the courtesy of Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.
‖Supplied through the courtesy of Sandoz A.G., Basel.

We studied the effect of epinephrine in the media at a concentration of 0.5 gammas/ml. on the binding of insulin-I^{131} at 2 x 10^{-3} units/ml. concentration. The results are shown in table 2. There was no significant interference with the binding of the labeled insulin by the diaphragm, even though the rise in glucose consumption by the insulin was blocked.

TABLE 2

Effect of epinephrine on binding of labeled insulin by the rat diaphragm

Medium			Glucose utilization (mg. × 10^{-2} per hemidiaphragm in 90 min.)		Counts p. min. p. hemidiaphragm
Insulin mU/ml.	Epinephrine ugm./ml.	N	mean	SEM	mean
2	—	10	58.6		60.1
2	10	10	31.8		59.2
Depression caused by epinephrine			26.8	2.9	0.9

Effect of dilution in a model epinephrine-insulin system: A medium was prepared containing insulin in a concentration of 2 x 10^{-3} units/ml. and epinephrine 10^{-2} gamma/ml. The effect of this medium on glucose consumption was compared with the effect of the medium diluted five times. In the next experiment the diluted medium was compared in effect with the same medium after another five-fold dilution. The results are shown in table 3, where it is noted that a greater than expected insulin effect was found with increasing dilution.

DISCUSSION

Only a slight effect of epinephrine and norepinephrine upon the basal consumption of glucose by the diaphragm was noted in the absence of added insulin. Although the effects were significant in the range 1-10 microgm./ml., the results are somewhat at variance with those obtained by Walaas and Walaas.[9] The latter found a reduction in the basal glucose consumption from an average of 2.8 mg./gm./hr. to 1.9 mg./gm./hr. It should be noted that the basal glucose consumption in our experiments with epinephrine was about 1.7 mg./gm./90 minutes, which is considerably less than that in the experiments of Walaas and Walaas, suggesting that the activity in our experiments already might have been depressed by epinephrine in the diaphragms. It is noted that Walaas and Walaas used a longer washing time than we did. They might possibly have washed out endogenous epinephrine already present in the tissues and thus raised the basal consumption.

The depressing effect of epinephrine and norepinephrine upon the effect of insulin in increasing the glucose consumption of the diaphragm was noted in our experiments in concentrations much lower than those reported by Walaas and Walaas[9] and by Riesser.[10] If the physiological blood level for epinephrine is assumed to be about 0.001 gamma per ml.,[12,13] this level could be expected to produce an effect on glucose consumption of the diaphragm, especially when undiluted serum is used for the determination. Groen, v. d. Geld and Willebrands[8] have noted that higher values for plasma insulin-like activity are obtained for serum diluted ten times than for whole serum. It is quite possible that the dilution of plasma adrenalin that occurs in this way might account for the nonlinearity of the insulin on serum dilution. For example, if a plasma adrenalin level of 10^{-2} gammas/ml. is present with a given insulin activity and the plasma is diluted ten times, the adrenalin level in the medium becomes 10^{-3} gammas/ml. From the curve (figure 1) however, this dilution of the adrenalin could be expected to produce a change in the inhibitory effect from about 90 per cent to about 50 per cent. Assuming that the per-

TABLE 3

Effect of dilution on the recovery of insulin activity in model insulin-adrenalin solutions of known concentrations

Insulin Conc. mU/ml.		Epinephrine Conc. ugm./ml.		D = Difference in glucose consumption between test and control (mg. × 10^{-2} p. 90 min. p. hemidiaphragm)	P	Insulin* activity in test (per cent of control)	Theoretical per cent activity
Control	Test	Control	Test				
2.00	0.40	.0100	.0020	—7.6 ± 4.3	0.15	38	20
0.40	0.08	.0020	.0004	—6.8 ± 2.4	0.05	42	20

*Calculated from: $100 \times \text{antilog} \frac{D}{17.8}$[6]

centage of depression is independent of the insulin concentration in the range to be expected (10^{-4} to 10^{-2} units/ml.), this might result in a serum insulin value, calculated from the diluted serum, that is five times the value calculated from the undiluted serum. Actually this type of relationship was demonstrated in the model dilution experiment shown in table 3.

The above considerations may be of clinical importance, particularly in some cases of insulinoma, where even while the blood sugar was quite low, normal or even low plasma insulin levels sometimes have been found.[3] Such patients with low blood sugars could be expected to have high epinephrine levels,[13,18,22,28] which would vitiate the results of plasma insulin determinations by the rat diaphragm method.

The anti-insulin effect of norepinephrine was surprising but is probably not significant at physiological levels.

The endogenous epinephrine levels of the test animal must also be reckoned with, though at the present time they cannot be controlled in this assay technic, since the adrenergic blocking agents in the medium did not change the epinephrine depression. It is quite possible that the presence of variable amounts of epinephrine in the diaphragms may account for some of the variation between animals.

Finally, the fact that the insulin activity of the plasma is suppressed in a manner similar to that of pure insulin, by epinephrine and norepinephrine, is further evidence that the plasma "insulin" activity as seen in the diaphragm test is actually due to insulin.

As to the mechanism of the inhibition of the glucose utilization, the possibility that epinephrine interferes with adsorption of insulin in the muscle cell (a process shown by Stadie et al.[10] to be important in its biological action) can be ruled out, in view of the absence of any change in the binding of labeled insulin to the diaphragm.

It seems probable that the inhibition is only indirect. As has been shown by Sutherland and Cori,[8,11] epinephrine causes an increase in concentration of active phosphorylase. This increases the breakdown of glycogen, with formation of lactic acid via glucose-1-phosphate and glucose-6-phosphate. Recently Weil-Malherbe and Bone[19] and Crane and Sols[20] found that glucose-6-phosphate inhibits the hexokinase reaction in a noncompetitive way. Therefore an increase in the concentration of glucose-6-phosphate caused by glycogenolysis would lead to decreased phosphorylation of glucose and diminished utilization of glucose from the medium.

SUMMARY

The stimulation of glucose utilization of the isolated rat diaphragm by insulin is strongly suppressed by very small amounts of epinephrine or norepinephrine; 10^{-2} microgm. of epinephrine was found enough to counteract almost completely the effect of 0.5 milliunits of insulin.

The significance of these findings for the determination of serum insulin by the use of the isolated rat diaphragm, especially in some cases of hyperinsulinism, is discussed.

Various sympathetic blocking agents tested showed no reversal of the suppression caused by epinephrine on the insulin effect on glucose utilization. Epinephrine does not interfere with the binding of labeled insulin to the diaphragm tissue.

SUMMARIO IN INTERLINGUA

Le Effecto Anti Insulina De Epinephrina: Su Signification Pro Le Determination De Insulina Seral Per Le Methodo A Diaphragma De Rattos

Le stimulation del utilisation de glucosa producite in isolate diaphragmas de ratto per le presentia de insulina es fortemente supprimite per micrissime quantitates de epinephrina o norepinephrina. Esseva constatate que 10^{-2} de epinephrina sufficeva pro contrariar quasi completemente le effecto de 0,5 milliunitates de insulina.

Es discutite le importantia de iste factos pro le determination de insulina in le sero per medio de isolate diaphragmas de ratto, specialmente in certe casos de hyperinsulinismo.

Varie agentes de blocage sympathic esseva testate e monstrava nulle reversion del suppression que epinephrina effectua in le influentia de insulina super le utilisation de glucosa. Epinephrina non obstrue le ligation de marcate insulina per le histos del diaphragma.

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The Revolution in Pharmacology

Until very recently, the course of progress in the discovery of new drugs has depended on chance. The history of pharmacology shows that the first member of a series of useful agents has been picked up accidentally. The usual course of events cannot be illustrated better than by examination of the circumstances which led to the introduction of reserpine and other *Rauwolfia* alkaloids and of chlorpromazine.

The medicinal use in India of extracts of the plant *Rauwolfia serpentina* dates back many centuries. Undoubtedly, its virtues, real or supposed, arose from the observation that ingestion of parts of this plant was beneficial in certain diseases. After many hundreds of years this empirical information impressed itself on the Western world, and an intensive effort was begun about 1950 in Switzerland and in the United States to extract from this plant its active ingredient, to isolate it in pure form, and to find out what its chemical structure was. This was finally accomplished in 1954 with the establishment of the chemical structure of the most active constituent, viz., reserpine. *Rauwolfia* alkaloids were introduced into Western medicine for the treatment of high blood pressure. Quite incidentally it was found that these drugs also calmed excitable animals and human beings, and this observation led to widespread trials of reserpine as a tranquilizing agent for mental patients. Medical practitioners of India had long ago noted this tranquilizing action of the plant and had used it on mental patients. The important point for the present discussion is that the introduction of these alkaloids into medicine was the result of chance observation. The chemical, biochemical, and pharmacological studies—in other words, the scientific investigations—were predicated on these chance discoveries. During these scientific studies, several new and apparently useful properties of the drugs were uncovered, but again quite by chance.

By D. W. Woolley, from *Perspectives in Biology and Medicine*, Vol. 1, No. 2, page 174, Winter 1958.

Immunologic Studies of Insulin in Man

Effect of Heat on Allergenicity

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Although 20 per cent of diabetic persons develop localized redness, induration and discomfort during insulin therapy, this tendency abates spontaneously after the first few weeks of daily treatment.[1] Occasionally, however, the allergic reaction is so intense and widespread as to contraindicate use of the hormone. In this event, several corrective steps are available. The need for insulin can, for example, sometimes be circumvented by rigorous dietary control. In other instances, it is only necessary to transfer to another brand, to a preparation which has been subjected to several recrystallizations,[2] to insulin derived from a different animal source, or—according to Dolger[3]—to the simple device of boiling the patient's supply of crystalline hormone for one hour. A more complicated alternative is to effect a rapid[3] or a gradual[4,5] "desensitization" (actually, active immunization).[5,6] The present study explores the claim that the allergen, insulin, can be denatured by heat. Aliquots of commercially available crystalline zinc insulin derived from swine and/or beef were exposed to temperatures of 60° or 100° C. for periods ranging from one to twenty hours. Samples were then tested for whealing activity in sensitized human skin, as well as for their capacity to neutralize allergic serum as judged by challenge tests with unheated insulin in modified Prausnitz-Küstner experiments.[6]

MATERIAL AND METHODS

Sources of Insulin-Allergic Serum: Two middle-aged women with moderately severe diabetes mellitus and with extreme insulin allergy (generalized urticaria and hypotensive shock from small therapeutic doses) supplied the blood needed for passive sensitization of normal subjects. Venipuncture was done in the fasting state at a time when no insulin had been used for treatment or tests for at least twenty-four hours. The sterile serum was stored at 6° C. without prior filtration or the addition of preservative.

Skin-sensitizing activity of the two sera was determined in the prospective test subjects by introducing 0.1 cc. into replicate sites along the posterior aspect of the thorax. In some experiments undiluted serum was employed, in others graded dilutions were injected, and in still others graduated strengths of insulin were mixed with a uniform volume of undiluted serum prior to injection. Twenty-four hours later, the previously prepared areas were challenged with heated or with unheated insulin in amounts and strengths controlled so that the reactivating powers of the two could be compared. Challenging solutions were, of course, concurrently examined in areas of unprepared skin to reveal any irritating qualities they might possess.

Test subjects were three healthy males in their early twenties. None had received insulin up to the time of the experiments. In each, 0.1 cc. of diluted 1:3 sensitizing serum was injected endermally to provide an area which, when later injected with .02 cc. of crystalline zinc insulin containing 4 units per cc., responded with a wheal which measured about 1 cm. in diameter and a surrounding flare 2 cm. wide (our three plus reaction), while a control test with 20-unit per cc. material gave no reaction in unprepared skin. An equal volume of insulin in concentrations of 10 to 40 units per cc. served to exhaust the transference powers of either serum for these subjects. Areas prepared with 0.1 cc. of plain serum responded promptly to concentrations of insulin as low as 0.0002 units per cc. These preliminary data surrounding the sensitizing sera and unheated insulins indicated that the experimental materials and subjects were both highly satisfactory for the purpose in hand.

RESULTS

Subject NEL, sensitized with 0.1 cc. of WEI 1:3 serum on the preceding day, responded maximally to .02 cc. of unheated crystalline zinc insulin 4 units/cc., derived from mixed pork and beef sources as indicated in table 1. The response to a control test with 20-unit per cc. material in unprepared skin was negative. Whereas the results with porcine zinc insulin were confirmatory, the reaction in the sensitized area was only about half as large when crystalline zinc insulin (beef) was the challenging antigen. This suggested that most of the reaction elicited by the pork and beef mixture was refer-

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TABLE 1

Influence of heating on activity of insulin in passively sensitized skin

Sensitizing Mixture			Response to Challenge Tests Done in 24 Hours					
			Sensitized areas			Unprepared skin		
Allergic serum 0.033 cc.	Insulin 0.033 cc.	Diluent 0.033 cc.	Insulin type	.02 cc. heating	Reaction at 20 min.	Insulin type	.02 cc. heating	Reaction at 20 min.
Test Subject NEL on 4/14 and 4/21/53								
WEI 2/3/53	isotonic salt	saline	P&B CZ4	0	3 red	P&B CZ20	0	0
"	isotonic salt	saline	Beef CZ4	0	1¾ red	Beef CZ4	0	1 pale
"	isotonic salt	saline	Pork CZ4	0	3— red	Pork CZ4	0	½ red
"	isotonic salt	saline	Beef CZ20	0	2— red	Beef CZ20	0	1¼ pink
WEI 2/3/53	isotonic salt	saline	P&B CZ4	1 hr. 60°	3½ red	P&B CZ4	1 hr. 60°	1— pink
"	isotonic salt	saline				P&B CZ20	1 hr. 60°	1¾ red
"	isotonic salt	saline	P&B CZ40	2 hr. 60°	3½ red	P&B CZ40	2 hr. 60°	1¼ pink
"	isotonic salt	saline	P&B CZ40	4 hr. 60°	3¼ red	P&B CZ40	4 hr. 60°	1¾ pale
"	isotonic salt	saline	P&B CZ40	4 hr. 60°	3— red			
WEI 2/3/53	P&B CZ40 1 hr. 60°	saline	P&B CZ4	1 hr. 60°	1— pink	P&B CZ4	1 hr. 60°	1— pink
"	P&B CZ40 1 hr. 60°	saline	P&B CZ4	0	1¾ red	P&B CZ4	0	0
"	P&B CZ80 4 hr. 60°	saline	P&B CZ10	4 hr. 60°	1— pale	P&B CZ10	4 hr. 60°	0
"	P&B CZ80 4 hr. 60°	saline	P&B CZ10	4 hr. 60°	1— pink			
"	P&B CZ80 4 hr. 60°	saline	P&B CZ4	0	½			
Test Subject LUD on 4/28/53								
WEI 2/3/53	isot. salt	isot. salt	P&B CZ4	0	2½ red	P&B CZ4	0	0
"	isot. salt	isot. salt	P&B CZ10	0	2¾ red	P&B CZ10	0	0
"	isot. salt	isot. salt	P&B CZ4	2 hr. 60°	2¾ red	P&B CZ4	2 hr. 60°	0
"	isot. salt	isot. salt	P&B CZ10	2 hr. 60°	2¾ red			
"	isot. salt	isot. salt	P&B CZ4	4 hr. 60°	2— red	P&B CZ4	4 hr. 60°	0
"	isot. salt	isot. salt	P&B CZ10	4 hr. 60°	2 red	P&B CZ10	4 hr. 60°	0
WEI 2/3/53	P&B CZ40 4 hr. 60°	isot. salt	P&B CZ4	2 hr. 60°	0			
"	P&B CZ40 4 hr. 60°	isot. salt	P&B CZ4	4 hr. 60°	0			
"	P&B CZ40 4 hr. 60°	isot. salt	P&B CZ4	0	0			
"	P&B CZ40 0	isot. salt	P&B CZ10	0	0			
"	P&B CZ40 0	isot. salt	P&B CZ4	2 hr. 60°	0			
"	P&B CZ40 0	isot. salt	P&B CZ4	4 hr. 60°	0			

able to its pork insulin component. Control tests revealed that there were mild irritating qualities in both of the unmixed preparations.

When the 4-unit per cc. mixture was similarly tested after heating, the specific reaction was undiminished while the control reactions indicated that mild irritative qualities had been acquired during the hour of heating at 60° C., particularly when 20-unit per cc. solution was employed. Heating for another hour introduced no further change in the pork and beef insulin mixture. However, extension of the heating period to four hours in the water bath may have reduced the urticariogenic activity suggestively for sensitized skin.

The antibody-neutralizing power of the aliquots heated one and four hours was next examined. A site previously prepared by injecting an equal mixture of WEI serum and 40-unit per cc. mixed pork and beef insulin that had been heated at one hour at 60° proved unresponsive when challenged with 4-unit per cc. material prepared from the same vial, only a borderline reaction of irritative nature being observed. When, however, an identical area was tested with unheated 4-unit concentration of insulin, the resulting wheal was only half the size of that obtained during the earlier experiments in conventionally prepared skin. This relationship was confirmed when higher concentrations of insulin that had been heated to 60° C. for four hours were similarly employed in the initial mixtures. Indeed, the homologous antigen in 10-unit strength provoked nothing more than an irritative reaction of small size in duplicate experiments. Furthermore, the great excess of heated insulin in the preparatory mixtures now sufficed to all but extinguish the responsiveness of the area to challenge with unheated insulin of 4-unit strength.

These findings revealed little or no reduction by heat of the urticariogenic qualities of insulin in sensitized skin. Whereas absorption of the serum with heated insulin removed its capacity to sensitize skin toward heated hormone, it also reduced markedly the response to unheated insulin, indicating that heated insulin possessed considerable residual neutralizing power. Indeed, if heated insulin of 80-unit concentration was selected

for the absorption, only a borderline challenge response could be elicited with the original insulin. Hence, any reduction in neutralizing power during heating was limited in extent.

Results were very similar when the same materials were examined about a week later in subject LUD; viz., the whealing power of the mixed insulin was unaltered by two hours of heating but was slightly reduced by four hours of exposure to heat. The neutralizing activity of the long-heated insulin showed no detectable change, sites prepared with absorbed serum failing to respond to any test with either heat-inactivated or unheated antigen. No irritative qualities were detected.

The second donor's serum was examined in normal subject, QUE, on January 3, 10 and 24, 1956, about a month after the blood had been drawn. Crystalline insulin (beef) of 40-unit per cc. strength was employed in areas that had been prepared with 0.1 cc. of SHO 12/12/55 serum and again in control sites that had received the normal serum of VAN 3/14/55. Although the original insulin provoked whealing that was recorded as 2¾ and possessed no irritative qualities, the aliquot heated at 100° C. for an hour evoked an identical response in the sensitized skin but was provocative of a 1¾ irritative reaction in the VAN control site. Thus the specific activity of the heated insulin was essentially the same as that associated with the unheated sample. A type of control absorption study was now carried out to complete the data given in table 1; i.e., *un*heated insulin was used to absorb the sensitizing activity from allergic serum. When sites prepared with this mixture were subsequently challenged with 40-unit per cc. insulin, only the irritative response was evoked by the boiled hormone, and the reaction was negative when unheated material was tested.

Having thus established in the three foregoing experiments that unheated insulin completely inactivated sensitized skin toward either heated or unheated insulin and that heated antigen was almost as effective as an absorbing agent, we attempted to make a final comparison between the unheated and the heated insulin by seeking to determine the minimal reactive strength of each in sensitized skin. The serum employed had been obtained from SHO on 11/27/54 and the test-subject, COA, was highly responsive. There appeared to be no appreciable reduction in allergenicity by water-bath exposures ranging from 5½ to 20 hr. at 60° C., whealing being comparable to that provoked by unheated samples (see table 2). Consequently, the insulin was heated at 100° C. so that the experiment could be repeated a month later. The reduction in activity was so slight as to be equivocal, concentrations in the fourth decimal units per cc. again proving effective.

DISCUSSION

The foregoing studies in passively sensitized skin revealed that heating at 60° C. or 100° C. injured the urticariogenic and the antibody-neutralizing activities of crystalline zinc insulin of beef and of pork origin so slightly as to be almost negligible. This was unexpected in view of the encouraging report of Dolger[1] who believed that his insulin-allergic patients were tolerant of

TABLE 2

Influence of heating on activity of insulin in passively sensitized skin (test subject, COA, prepared with 0.1 cc. SHO 11/27/54 insulin-sensitive serum). Responses to challenge tests done in 24 hours with beef CZ Insulin .02 cc.

Heating period of insulin	Reactions to Various Strengths in Sites							Reactions in Control Areas		
	.00014	.0005	.0016	.009	.019	.625	1.25	Unprepared .625	Skin 2½	Normal Serum .0016
Experiment of 3/29/55										
5½ hr. 60°	1	1½		2¾		2¾		0		
14½ hr. 60°		¾				2¾		0		
20 hr. 60°		1¾				3—		0		
Unheated	½	1½		2½	2¾			0		
"		1½		2—				0		
Experiment of 4/29/55										
1 hr. 100°			½				¾			0
4 hr. 100°		1¼				1¼				0
Unheated		1½		2½		2		0	0	0

insulin that had been "denatured" by thirty minutes of boiling and could be desensitized with it during a few weeks to the point that no commercial insulin would provoke untoward reactions. He was further encouraged by the communication of Peck[16] that regular and crystalline zinc insulin in acid medium (*p*H 3) retains over half of its physiologic activity after three hours of boiling in a reflux condensor. In view of the simplicity of Dolger's device, it is disappointing that our laboratory experiments with heated insulin fail to support his ingenious suggestion. There is no question that his patients acquired immunity during their injections with heated insulin. It seems likely, however, that he would have had about the same result had unheated insulin been employed. Indeed, carefully graduated doses of commercial or of eight-times recrystallized insulin provided an exquisitely allergic woman with a normal tolerance within some weeks.[5] This tolerance was found to depend on her development of blocking antibodies which competed with the allergic antibodies she possessed in her plasma, skin and conjunctivae. These heat-stable antibodies bound the insulin without causing any tissue reaction, thereby preventing the insulin from being combined with the sensitizing antibodies.

Lowell[4] was the first to propose the existence of two types of antibody for insulin in man, pointing out the analogy between this dual response and that described[9] for pollen-allergic individuals following their completion of a series of immunizing injections. Although tolerance has been built up in insulin-allergic patients by numerous physicians, their use of the term, desensitization, has implied that success rests on a saturation or neutralization of the patient's allergic antibodies. Actually, as Lowell surmised and as our experiment revealed, the mechanism is one of blocking antibody development. Since this antibody is not only anti-allergic[5] in its clinical effect but is also antihormonal, as judged by insulin tolerance tests in either mouse or man,[4,5] it must be assumed, until the matter has been elucidated by further study, that the immunized patient may be protected not only against his allergy but also, unfortunately, against the physiologic action of administered insulin. Is immunization, in this event, justifiable?

Whether the blocking antibody, and indeed the allergic antibody, are directed against the same grouping on the insulin molecule as that responsible for its hormonal action can only be conjectured. Lowell[7] made the observation that cysteine-inactivated insulin was still capable of uniting with insulin-antibody procured from the rabbit. It was therefore logical to infer that the antihormonal activity of the antibody rested on steric hindrance rather than on combination with the physiologically active groupings of the molecule (the latter having been chemically altered by cysteine). In view of the disparity between the molecular weight of insulin (12,000[8] or 6,000[9,10]) and those of the gamma globulins and beta globulins of human serum (which have molecular weights of at least 150,000), it would not be surprising if the blocking antibody, a modified gamma globulin,[11] and the allergic antibody, a modified beta globulin,[12] were to overlap the hormonally active area of insulin when complexed with this antigen. On the other hand, there is no evidence that the allergic antibody can unite with its antigen except in the vicinity of such tissue as the skin,[13] whereas the blocking antibody rapidly binds its antigen in vitro[14,15] and, by inference, in the bloodstream and tissue fluids. In the former situation, the physiologic action of insulin might theoretically occur before the insulin reached the sensitized cells, whereas in the latter instance the antigen-antibody combination might precede and thereby preclude such action. Lowell[4] noted no clinical evidence of diminished hormonal response to administered insulin when his patient was showing allergic reactions. This stood in contrast to other periods when there were no untoward manifestations but large amounts of insulin were required to control the diabetes in the presence of blocking antibody.

CONCLUSIONS

1. Dolger's conclusion that insulin can be rendered essentially nonallergenic by heating could not be substantiated when the hormone was tested in passively sensitized skin. Water-bath temperatures of 60° C. maintained for one to twenty hours and of 100° C. for one to four hours exerted little or no influence on the whealing activity of crystalline pork and/or beef insulins. Furthermore, the antibody-neutralizing power of such samples was only slightly less than that exhibited by unheated aliquots. There would seem to be little advantage, therefore, in substituting heated for unheated insulin when combating extreme insulin allergy by means of multiple, small injections that elevate the patient's tolerance. With either agent, the mechanism is blocking antibody development, or active immunity—not "desensitization," in the strict sense of the term.

2. Some speculations are made concerning the physiologically active areas of the insulin molecule, on the one hand, and the antigenic areas of the molecule that are responsible for the stimulation of allergic and of blocking (or resistant) antibodies, on the other. It

seems likely that the much larger antibody molecules could readily impose steric hindrance on the physiologic activities of the small insulin molecule, providing complexing preceded the hormonal action and despite the possibility that different groupings on the insulin molecule might be involved in the immunologic and hormonal actions.

SUMMARIO IN INTERLINGUA

Studios Immunologic De Insulina In Humanos
I. Effecto De Calor Super Le Allergenicitate

1. Le conclusion de Dolger, i.e. que insulina pote esser rendite essentialmente non-allergene per calefacer lo, non esseva corroborate quando le hormon esseva testate in pelle passivemente sensibilisate. Calefaction in banio de aqua al temperatura de 60 C durante periodos ab 1 a 20 horas e al temperatura de 100 C durante periodos ab 1 a 4 horas exerceva pauc o nulle influentia super le activitate de vibication de crystallin insulina porcin e/o bovin. In plus, le potentia de neutralisar anticorpore se monstrava solmente pauco reducite in specimens tractate assi quando comparate con ille potentia in correspondente specimens non–calefacite. Ergo il non pare multo avantagiose servir se de calefacite in loco de non–calefacite insulina in combatter extreme grados de allergia a insulina per medio de micre e multiple injectiones destinate a elevar le tolerantia del patiente. Le mechanismo per que le agente exerce su effecto es le mesme in ambe casos. Il se tracta de blocage del disveloppamento de anticorpore, i.e. de immunitate active—non de "dissensibilisation" in le senso precise del termino.

2. Es presentate certe speculationes relative a (1) le physiologicamente active areas del molecula de insulina e (2) le areas antigenic del molecula que es responsabile pro le stimulation del disveloppamento de anticorpore allergic e blocante (o resistente). Il pare plausibile que le molecula de anticorpore (que es multo plus grande que le molecula de insulina) es capace a imponer un obstruction steric super le activitate del micre molecula de insulina, providite que complexation precede le action hormonal e in despecto del possibilitate que varie gruppamentos intra le molecula de insulina es interessate in le processo immunologic e hormonal.

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Fourteen-day Administration of Carbutamide, Tolbutamide and Cortisone

Effects on Metabolism of Rat Liver and Diaphragm

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Much of the recent work on the effects of oral hypoglycemic agents has involved measurements in animals after a brief period of treatment with the drug. In general, it has been concluded that there is no direct effect of these drugs in enhancing glucose utilization of the peripheral tissues. Studies on the isolated rat diaphragm have confirmed this conclusion, since added sulfonylurea did not enhance the glucose uptake or glycogen synthesis of that muscle in vitro.[1-3] Studies in vitro of liver slices also have suggested that the sulfonylureas exert an inhibiting effect upon glycogenolysis[1,4] though under certain conditions tolbutamide seemed to affect only the potentiating effect upon glycogenolysis of epinephrine or of glucagon.[5] Some workers have felt that the levels of drug required to give an in vitro effect are so high that this effect cannot be considered of physiological significance.[6]

We have studied certain changes resulting from a more prolonged administration of carbutamide or of tolbutamide in the rat. A previous report by Root[7] indicated that if tolbutamide were given for a period of time, rather than as a single dose, there was a reduction in the extractable insulin of the pancreas, a reduction in liver glycogen, and in some cases a fall in muscle glycogen. Root interpreted these results with caution, since but few animals were used, and some of the treated animals were in poor condition. Candela and Candela have reported that carbutamide, given orally to rats four hours before sacrifice, caused an increased glucose uptake of the diaphragm[8] but that the stimulating effect of added insulin was unaffected.[9] Miller, Krake and Van der Brook also have shown that six hours after the administration of tolbutamide, there is an increased incorporation of glucose in muscle glycogen.[10]

We have found that glycogen levels in the rat diaphragm were significantly increased by carbutamide administration over a period of time. This may conceivably be a consequence of increased plasma insulin activity. Liver glycogen values were not significantly changed as a result of carbutamide administration. Liver fat was increased by cortisone. Tolbutamide, in general, did not seem to exert any effect on glycogen levels in liver or diaphragm. This may be a consequence of not giving enough tolbutamide, though the doses of tolbutamide and of carbutamide were the same on a weight basis, and very nearly the same on the basis of molecular weight.

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MATERIALS AND METHODS

A group of fifty-four male Wistar rats, weighing 200-225 gm., was divided into six equal subgroups. Each group was given a daily subcutaneous injection for fourteen to fifteen days, as shown below:

Group 1—1.0 ml. saline (control group).
Group 2—50 mg. carbutamide (approx. 250 mg./kilo body weight).
Group 3—50 mg. carbutamide plus 10 mg. cortisone.
Group 4—50 mg. tolbutamide (approx. 250 mg./kilo body weight).
Group 5—50 mg. tolbutamide plus 10 mg. cortisone.
Group 6—10 mg. cortisone (approx. 50 mg./kilo body weight).

The cortisone was given as 0.4 ml. of Merck's "Cortone," containing 25 mg. cortisone acetate per ml. Carbutamide and tolbutamide were dissolved in alkaline solution to give a 4 per cent solution. When solution was completed, the *p*H was adjusted to 7.5 with hydrochloric acid. For one experiment, one animal in each group was used, so that a total of nine replicate experiments were performed on nine different days.

At the end of the injection period, the animals were fasted for twenty hours. Fasting increases the glucose uptake and the glycogen synthesis in the isolated diaphragm, in the absence of insulin, and seems to yield results with a somewhat smaller spread of values.[11] The animals were then decapitated and tissues were removed for the various studies. In some of the animals, a portion of the liver was weighed and used for a determination of the nitrogen by the micro-Kjeldahl method. Two other

portions were rapidly weighed, and dropped into hot KOH for a determination of liver glycogen according to the method of Good, Kramer and Somogyi.[12] The remainder of the liver was used for a determination of the liver fat, according to the method of Best, Lucas, Patterson and Ridout.[13] The diaphragm was removed and divided into three portions. One portion, which usually weighed between 70 and 90 mg., was used for a determination of the initial glycogen content. The other two, which usually weighed between 100 and 120 mg., were incubated in a Gey-Gey medium,[14] with 200 mg. per cent added glucose. (One portion acted as a control, the other was incubated with added insulin, 1 unit/ml.). Tissues were placed in 10 ml. of medium in 25 ml. flasks, and were shaken in air, at 37° C., in a Dubnoff shaker for one hour. The tissues were then removed, blotted and put into hot KOH for a determination of glycogen. One ml. aliquots were removed from the incubation media for the determination of the glucose concentration, according to the method of Somogyi.[15]

From the "final glycogen" values obtained in the tissues after incubation, the "initial glycogen" values were subtracted, and these are the values shown as "glycogen difference" in table 2. A positive value indicates that there was net glycogen synthesis, a negative value indicates that the process of glycogen breakdown predominated over those processes leading to glycogen synthesis. The "insulin effect" on either glycogen synthesis or glucose uptake is the difference between values obtained with hemidiaphragm incubated in a medium with added insulin, and values obtained with a diaphragm incubated in a medium without added insulin.

RESULTS

The results of the liver analyses are seen in table 1. Cortisone increased the liver fat, but there was no significant effect of either carbutamide or of tolbutamide on liver fat. The percentage of nitrogen in the liver was unaltered by any of the other treatments. Cortisone increased liver glycogen, but the other drugs did not have any significant effect.

The results from the analyses of the diaphragms are

TABLE 1
Results of liver analyses

	Control	Carbutamide	Tolbutamide	Cortisone	Carbut. + Cortisone	Tolbut. + Cortisone
Glycogen (mg./gm.)	1.78± 0.50	1.74 ±.11	1.75 ±.26	16.90 ±2.51	15.20 ±1.40	18.89 ±1.93
Nitrogen (mg./gm.)	38.4 ±.84	37.1 ±.29	37.1 ±.39	38.2 ±1.00	37.5 ±.51	37.1 ±1.43
Fat (per cent dried fat-free residue)	32.1 ±1.18	34.6 ±1.54	35.0 ±1.39	42.1 ±3.74	49.2 ±6.40	42.5 ±2.38

TABLE 2
Results of diaphragm analysis

	Control	Carbutamide	Tolbutamide	Cortisone	Carbut. + Cortisone	Tolbut. + Cortisone
1. Initial glycogen (mg./gm.)	0.88	1.15	1.12	1.87	2.33	1.93
2. Glycogen difference (mg./gm.)	0.25	—0.01	0.10	—0.53	—1.10	—0.67
3. Insulin effect on glycogen synthesis (mg./gm.)	0.47	0.72	0.68	0.61	0.93	0.86
4. Glucose uptake without insulin (mg./gm.)	5.23	5.44	4.49	5.24	5.52	5.10
5. Insulin effect on glucose uptake (mg./gm.)	1.72	1.37	2.14	2.01	1.32	1.68

shown in tables 2 and 3. Average results are shown in table 2, and table 3 gives a summary of the results of the statistical procedures which were applied to the experimentally determined values.

The design and analysis of the experiment is in the form of a simple split-plot experiment.[16] The significance of the effect of the cortisone treatment may be obtained directly from the table of the analysis of variance by dividing the mean square for cortisone treatment by the mean square for error (a). The significance of the effect of tolbutamide is obtained by finding the difference between the mean values obtained from all animals treated with tolbutamide and the mean values from animals whose treatment was similar, except that they were not treated with tolbutamide. This difference is compared with an estimate of the error of the determination, as in a "t" test. The significance of the effect of carbutamide is similarly calculated.

In line 1 of table 2 there are shown the amounts of glycogen in portions of diaphragm which were removed immediately after sacrifice of the rat. The statistical analysis of the results (see table 3) shows that pretreatment with carbutamide or with cortisone significantly increased the initial concentration of muscle glycogen. No such effect was seen from the pretreatment with tolbutamide.

In line 2 of table 2 are seen the "Glycogen Difference" values. In general, when there has been a high initial glycogen, the "Glycogen Difference" values are small and may even be negative. Figure 1 shows the relationship between glycogen differences and initial glycogen levels in the diaphragm.

The statistical analysis shows that pretreatment with cortisone or carbutamide significantly decreased the "Glycogen Difference." Tolbutamide had no significant effect. It is felt that the changes are probably reflections of the different initial glycogen levels, as indicated above.

In line 3 of table 2 the amounts of additional glycogen synthesized as a result of the presence of insulin in the medium are recorded. Cortisone, tolbutamide and carbutamide all significantly increased the insulin effect upon glycogen synthesis.

TABLE 3

Summary of results of statistical analysis according to split plot design

		Initial glycogen		Glycogen difference		Insulin effect on glycogen difference		Glucose uptake		Insulin effect on glucose uptake	
	d.f.	Mean square	F.	M.S.	F.	M.S.	F.	M.S.	F.	M.S.	F.
Replications	8	1.16	3.14	1.04	3.38	0.27	16.9*	14.1	12.6*	1.33	2.77
Cortisone treatment	1	13.25	35.8*	10.48	34.0*	0.42	26.1*	0.73	<1	0.08	<1
Error (a)	8	0.37		0.31		0.02		1.12		0.48	
Hypoglycemic agent treatment	2	0.63	3.30*	0.80	4.7*	0.40	3.92*	2.18	<2	1.78	<1
Interaction (agent × cortisone)	2	0.14	<1	0.13	<1	0.01	<1	0.49	<1	1.49	<1
Error (b)	32	0.19		0.17		0.10		1.16		1.76	
Standard error of difference between two treatment means for hypoglycemic agents		0.146		0.138		0.106					
Mean value (no hypoglycemic agent)		1.37		—0.14		0.54		Detailed analysis not performed since results above show there was no significant effect of hypoglycemic agents.			
Mean value (with tolbutamide)		1.52		—0.29		0.82					
t		0.15/0.15=1.0		0.15/0.14=1.08		0.28/0.106=2.64*					
Mean value (with carbutamide)		1.75		—0.55		0.77					
t		0.38/0.15=2.53*		0.41/0.14=2.97*		0.23/0.106=2.15					

*Results are significant at 5 per cent level or better.
Error (a) is used to test significance of "Replications" and of "Cortisone Treatment."
Error (b) is used to test significance of "Hypoglycemic Agent Treatment" and of "Interaction (Agent × Cortisone)."
"F" values less than 2 are not significant.

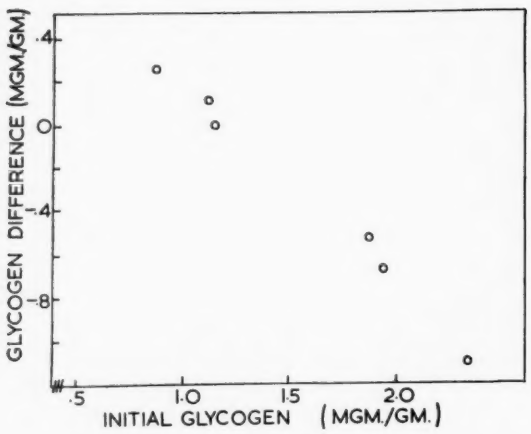

FIGURE 1

The glucose uptake of the diaphragm, as shown in line 4 of table 2 was not significantly altered by any of the treatments. Similar conclusions were reached regarding the insulin effect upon glucose uptake, as seen in the bottom line of table 2.

DISCUSSION

The increase in glycogen in the diaphragm caused by the pretreatment with carbutamide is consistent with the hypothesis of an increased effective insulin concentration in the plasma. This increase might come about through an increased secretion by the pancreas, or through a decreased activity of a plasma insulinase[17] or a decreased activity of a plasma insulin inhibitor. It would be expected that there might be an increased glucose uptake, but the experimental values do not show any such effect. There is no significant effect of pretreatment upon the insulin effect on glucose uptake, though the figures may suggest a reduction. Such a reduction would agree with the results reported by Field[3,18] for somewhat different experimental conditions. It may be, therefore, that carbutamide has no effect on a "basic" glucose uptake of the diaphragm, untreated by insulin, but that there is an inhibitory action of this compound upon the stimulating effect of insulin. This possible inhibition of the effect of insulin upon glucose uptake is difficult to reconcile with the significant increase in the insulin effect upon glycogen synthesis following carbutamide pretreatment, unless this agent favors those reactions leading to glycogen synthesis, relative to those which lead to glycolysis.

There is no significant effect of the hypoglycemic agents upon liver fat, though there does seem to be a suggestive trend in the figures. The direction of the trend is such as to be compatible with increased insulin activity. The effect of cortisone is highly significant, and is probably a consequence of the fat mobilizing action of the steroid. The amounts of nitrogen and of glycogen in the liver are unaffected by carbutamide or by tolbutamide, though cortisone gives the expected increase in glycogen. The lack of effect of hypoglycemic agents upon liver glycogen is in contrast to the decrease reported by Root[7] after administration of carbutamide to dogs, and the increase reported by Miller and Dulin[17] after administration of tolbutamide to rats.

In no cases did the cortisone seem to affect the action of the hypoglycemic agents, i.e., they seemed to act quite independently.

SUMMARY

1. The effects of subcutaneous administration of carbutamide and tolbutamide on certain aspects of carbohydrate metabolism in the rat have been studied.

2. The effect of cortisone upon the action of the above agents has been investigated.

3. Administration of carbutamide causes an increase in muscle glycogen. Net glycogen synthesis in the muscle after incubation in vitro in a glucose containing medium is reduced after treatment with carbutamide.

4. Liver glycogen, liver nitrogen and liver fat are not significantly altered by carbutamide treatment.

5. Cortisone caused an increased liver glycogen and increased liver fat.

6. Tolbutamide, in the dose levels given, only affected the insulin effect upon glycogen synthesis.

7. These results are consistent with the hypothesis that one of the effects of carbutamide is to cause an increased insulin activity in the plasma. It may be that there is an additional effect which tends to reduce the magnitude of the effect of this additional insulin upon the glucose uptake of the diaphragm.

SUMMARIO IN INTERLINGUA

Le Administration, Durante Dece-Quatro Dies, De Carbutamido, Tolbutamido, E Cortisona: Effectos Super Le Metabolismo Del Hepate E Diaphragma De Rattos

1. Esseva studiate le effectos del administration subcutanee de carbutamido e tolbutamido super certe aspectos del metabolismo de hydratos de carbon in le ratto.

2. Le effecto de cortisona super le action del supramentionate agentes esseva investigate.

3. Le administration de carbutamido causa un augmento de glycogeno muscular. Le nette synthese de glycogeno que occurre in le musculo post incubation in vitro in un medio que contine glucosa es reducite post

le tractamento con carbutamido.

4. Le glycogeno del hepate, le nitrogeno del hepate, e le grassia del hepate non es alterate significativemente per le tractamento con carbutamido.

5. Cortisona causava un augmento del glycogeno del hepate e del grassia del hepate.

6. In le doses usate, tolbutamido afficeva solmente le effecto de insulina super le synthese de glycogeno.

7. Iste resultatos concorda con le hypothese que un del effectos de carbutamido es le causation de un augmentate activitate de insulina in le plasma. Il es possibile que il existe un effecto additional que tende a reducer le magnitude del effecto de iste insulina additional super le acceptation de glucosa per le diaphragma.

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Human Experimentation

Biologic and medical investigation is accepted as essential to progress in health. Recent advances in the prevention, cure and treatment of diseases attest to the power and value of research. Today, the public and the professions alike agree that medical research must precede and then succeed practice to provide a basis for action and an evaluation of its worth. Such research, frequently in the most critical areas, takes the form of experimentation on human beings.

Development of standard diagnosis and treatment calls first for trial of novel methods. Ultimately, every innovation intended to benefit mankind must be tried on a human being—perhaps on thousands, as witness the trials with the Salk and the announced Sabin poliomyelitis vaccine—before it may be considered acceptable practice or procedure. Properly conducted experimentation by qualified scientists must therefore be considered an integral branch of biologic and medical science, but it does not thereby become customary medical practice. Nor does its essentiality and acceptance establish clearly its character or place the methods employed beyond scrutiny. The responsible professions have a duty to delineate for their own members and for a critically vigilant public the nature of medical research and the limits within which it may be properly undertaken.

From the article by Irving Ladimer, J.D., in *The New England Journal of Medicine,* July 4, 1957, pp. 18-24.

Effect of Carbutamide on Blood Levels of Glucose, Potassium and Inorganic Phosphate

Studies of the Serum in Diabetic and Healthy Man and Pancreatectomized Dogs

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I

Of the hormones influencing carbohydrate metabolism insulin, some steroids of the adrenal cortex,[1] and, according to some workers, adrenalin[2] bring forth an increase in K-level of the serum. It has been suggested in the literature that decrease in the K-level of the serum following insulin is partly due to enhanced glycogen synthesis in the liver and musculature, partly to increased sugar utilization.

In previous publications[3] the authors have presented evidence of the hypoglycemic effect of carbutamide* in diabetic subjects, and a favorable therapeutic response was seen in 71 per cent of our patients. This investigation was undertaken to determine whether the blood sugar changes occurring as an effect of carbutamide would be accompanied by changes in ion metabolism similar to those following hypoglycemia caused by insulin.

METHODS

After determination of an initial fasting blood sugar, serum-K and inorganic-P, the subjects were given 3 gm. Nadisan (carbutamide) per os, and these same determinations were repeated at 30, 60, 120, 180 and 240-minute intervals. The patients fasted throughout the examination. Blood glucose was determined according to the method of Schmör,[4] serum-K by the flame-photometer and serum-P by the Fiske-Subbarow methods.[5]

Carbutamide was considered effective if the fall of the blood sugar exceeded 20 per cent of the fasting value.[3] The change in serum-K level was considered significant if it was greater than 10 per cent of the control level, since it has been established previously in healthy individuals that the spontaneous serum-K level variation in four hours is within the ±10 per cent limit.

Our material was divided into three groups: 1. Twenty diabetics who responded to carbutamide. 2. Ten diabetics who showed no significant hypoglycemic response to carbutamide. 3. Control group of twenty patients with no demonstrable abnormality of carbohydrate metabolism.

RESULTS

In each of the twenty patients responding to carbutamide blood sugar fell over 20 per cent, as demonstrated by figure 1.

Serum-K determinations in seventeen of the twenty patients revealed decreases of more than 10 per cent. Decrease of the serum-K level paralleled the blood sugar fall.

There was not a single case among the ten unresponsive diabetics of a clinically effective, i.e., more than 20 per cent, blood sugar fall. The majority of this group consisted of young diabetics of the labile type (figure 3).

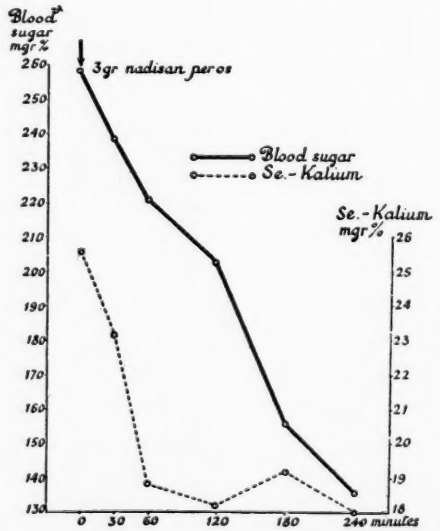

FIG. 1. Blood sugar and serum potassium change in diabetic patient responding well to Nadisan.

* BZ-55 (Nadisan or carbutamide).

From the First Department of Medicine, University Medical School, Szeged, Hungary.

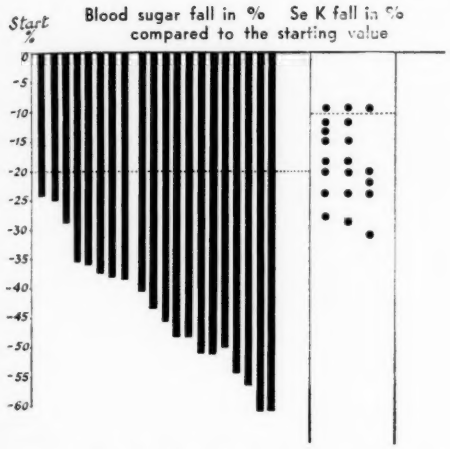

FIG. 2. Diabetic patients responding to Nadisan.

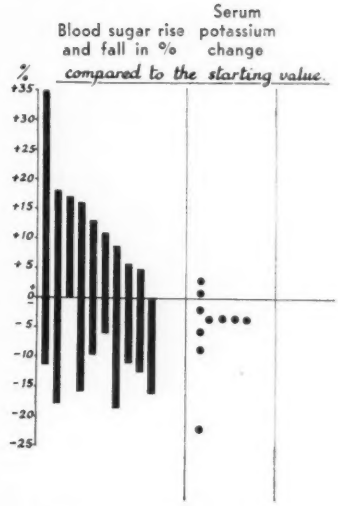

FIG. 4. Diabetic patients not responding to Nadisan.

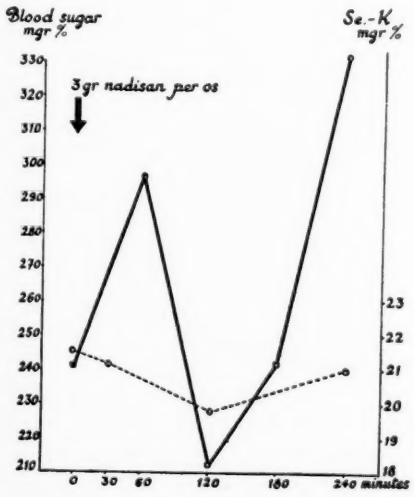

FIG. 3. Blood sugar and serum potassium change in a diabetic patient not responding to Nadisan.

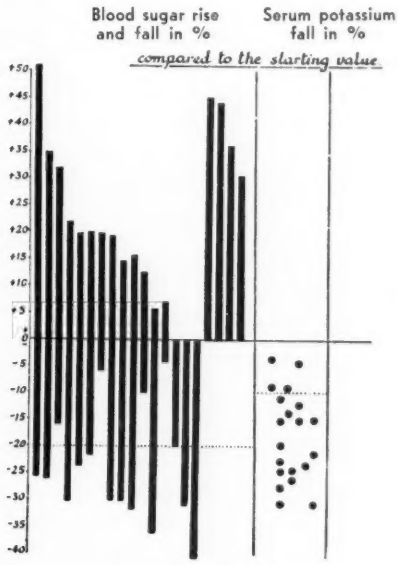

FIG. 5. Normal group.

There was no significant change in the serum-K level of these patients, as illustrated by figure 4. One case excepted, the fluctuation remained within the 10 per cent limit.

In the control group of twenty patients with normal carbohydrate metabolism, the blood glucose showed extreme fluctuation (figure 5) preceded by an initial rise; in others the initial blood sugar decrease was followed by a rise above the fasting level.

A prolonged decrease of blood glucose was seen in only three cases of the twenty experiments. Clinical hypoglycemia was not observed in any of the cases. While blood glucose decrease becomes more marked in responsive diabetic patients from hour to hour, the fluctuating blood glucose level in the normal subject suggests increased activity of the blood glucose regulating system. The serum-K level behaves like that of the responsive diabetic patients. As can be seen in figure 5,

the fall of serum-K exceeds 10 per cent in seventeen cases out of twenty.

Simultaneous serum inorganic-P determinations in all three groups showed no significant changes corresponding to the fluctuation of the blood glucose and serum-K levels.

DISCUSSION

Mohnike and Bibergeil[9] formerly reported changes of serum-K and inorganic-P occurring after administration of D-860 in the normal dog. In their experiments there was a parallel decrease in both serum-K and blood sugar; on the other hand, serum-P significantly rose after an initial fall. As is known from numerous publications[7-9] K is required for glycogen synthesis. Animal experiments of several workers [10-12] demonstrated that both carbutamide and tolbutamide increase the glycogen content of the liver. In patients responding to carbutamide, parallel decreases in serum-K and blood glucose might be explained by increased glycogen synthesis in the liver and subsequent glycogen deposition. It appears that in unresponsive diabetic subjects this glycogen synthesis in the liver is not increased enough to produce serum-K decrease. Serum-K decrease in normal individuals may be similarly explained by enhanced glycogen formation, despite the marked fluctuation of the blood sugar level after oral carbutamide, for which supposedly an increased compensating reaction of the adrenal may be responsible. It has been demonstrated in animals[13,14] that after substantial doses of sulfonylurea and IPTD, a pronounced hyperglycemia occurs which can be prevented by adrenalectomy. It is postulated that a similar mechanism is responsible for the failure to show a sustained decrease in blood glucose levels in the intact, nondiabetic human.

There was no change in the serum inorganic-P level in any group. This suggests that peripheral glucose utilization is not increased by the administration of Nadisan in the dose employed by us.

II

In the following an attempt has been made to elucidate what sort of changes do occur in blood sugar, serum-K and P after carbutamide administration in an organism deprived of endogenous insulin by pancreatectomy.

METHODS

Our experiments were performed on totally pancreatectomized dogs of 7 to 10 kg. body weight. Following operation the animals were maintained on a free diet and crystalline insulin. The experiments were performed at least two to three weeks following the operation. The animals obtained the last insulin dose forty-eight hours prior to the experiment and in addition were fasted for eighteen hours. After determination of fasting blood sugar, serum-K and P, 0.5 gm./kg. body weight of carbutamide was given intravenously. At intervals of 30, 60, 120, 180 and 240 minutes, samples of blood for glucose, inorganic serum-K, and -P determinations were taken. The animals were fasting throughout the experiments. Blood sugar was determined by the method of Somogyi, serum-K with a flame photometer and serum inorganic-P by the Fiske-Subbarow procedure.

RESULTS

Altogether sixteen experiments were performed on eight totally pancreatectomized dogs. Figure 7 illustrates the range of variation of blood sugar and serum-K expressed as per cent of the initial values. As can be seen, a significant blood sugar fall occurred six times; there was no change at all in six experiments, and in four there was a pronounced rise of blood sugar. The values shown in the blood sugar curve in figure 8 represent an average of all sixteen experiments; a successive decrease of blood sugar lasting until the fourth hour is seen, but this change does not appear to be statistically significant ($p>0.1$).

The effect of intravenous carbutamide on serum-K is shown in figure 7. In all but two cases a decrease is noted. A statistically significant decrease in the serum-K is seen to reach a minimum value in the fourth hour in figure 8 ($p<0.02$). The gradual rise of serum inorganic-P shown in figure 8 is statistically significant ($p<0.05$).

DISCUSSION

The experimental data here presented on diabetic and normal persons and pancreatectomized dogs tend to support the hypotheses stated in the literature that carbutamide increases glycogen synthesis in the liver but has no effect on peripheral glucose utilization.

In the mild type of diabetes mellitus, the secretion of endogenous insulin is not sufficient to maintain adequate carbohydrate metabolism. By means of mechanisms not yet elucidated, carbutamide, in the presence of endogenous insulin,[15,16] stimulates glycogen formation in the liver. As a consequence, glycosuria is diminished, resulting in amelioration of the diabetic symptoms. The endogenous insulin is needed not for the stimulation of glycogen synthesis but rather to maintain peripheral sugar utilization.

Our experiments are in accord with this hypothesis. The decrease of serum-K after the intravenous administra-

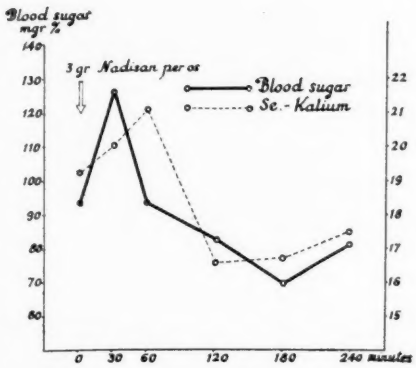

FIG. 6. Blood sugar and serum potassium change on effect of Nadisan in a normal individual.

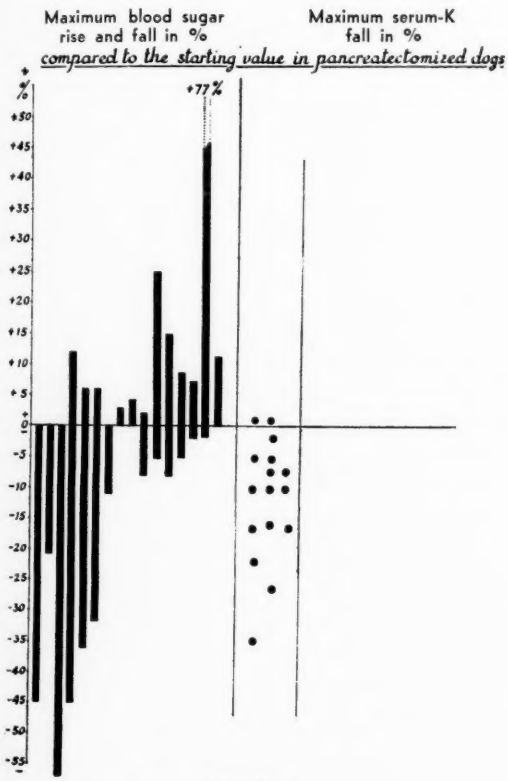
Maximum blood sugar rise and fall in %
Maximum serum-K fall in %
compared to the starting value in pancreatectomized dogs
+77%

FIGURE 7

tion of carbutamide in the pancreatectomized dogs suggests that there is a stimulus to deposition of glycogen, insufficient, however, to maintain the animal in carbohydrate balance. As can be seen in figure 8, there is some decrease in the blood sugar level of the animals,

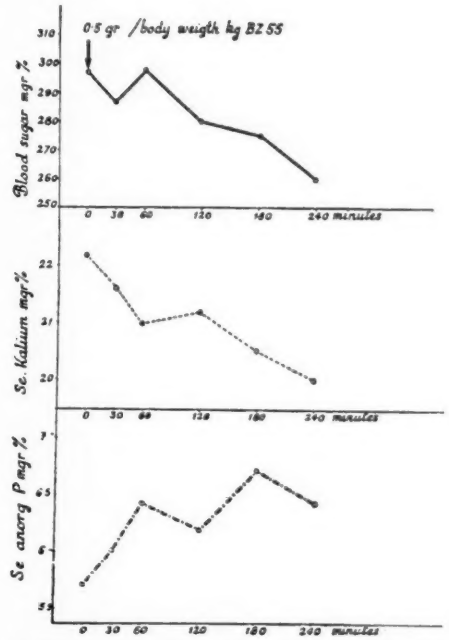

FIG. 8. Blood sugar, serum potassium and serum inorganic phosphorus change on effect of carbutamide in pancreatectomized dogs.

but since there is no peripheral utilization of glucose, suggested by the increasing inorganic-P levels, the organism progresses to increasingly severe carbohydrate decompensation.

These observations would explain why insulin must be present in order to develop significant hypoglycemia after the administration of carbutamide.

This interpretation is supported by an event that occurred during the experiments. A dog was erroneously given his usual insulin dose immediately after intravenous administration of carbutamide. Even though the animal was fed, he succumbed to hypoglycemia in two hours.

SUMMARY

We believe our investigations show that carbutamide, through its effect on glycogen synthesis, is able to maintain an organism in carbohydrate balance if the organism is producing some endogenous insulin. In the absence of this, i.e., the pancreatectomized subject, the help afforded by increased glycogen formation is far from sufficient, as peripheral sugar utilization is not affected by carbutamide. Thus the sulfonylureas, even though they are able to stimulate glycogen synthesis in the absence of insulin, are not effective in preventing ultimate diabetic coma unless insulin is also present.

SUMMARIO IN INTERLINGUA

Le Effecto Acute De Carbutamido Super Le Nivellos De Glucosa, Kalium, E Phosphoro Inorganic In Le Sero De Individuos Diabetic E Normal E De Canes Pancreatectomisate

Nos crede que nostre investigationes ha monstrate que carbutamido, per su effecto super le synthese de glycogeno, es capace a mantener un organismo in equilibrio carbohydratic, providite que le organismo produce un certe quantitate de insulina endogene. In le absentia de isto—i.e. in le individuo pancreatectomisate—le succurso representate per un augmento del formation de glycogeno remane nettemente insufficiente, proque le utilisation peripheric de sucro non es afficite per carbutamido. Assi le sulfonylureas—ben que illos es capace a stimular le synthese de glycogeno in le absentia de insulina—non es efficace in prevenir un ultime coma diabetic, excepte in caso que insulina es etiam presente.

ACKNOWLEDGMENT

We wish to express our thanks to Dr. A. Botos, first assistant, for the pancreatectomies and Mrs. J. Kahán and Mrs. I. Láng for their valuable assistance in laboratory determinations.

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The Use of Isotopic Tracers in Estimating Rates of Metabolic Reactions

Since the introduction of practical methods for the production and measurement of substances containing isotopes of elements common in biological systems—such as hydrogen, carbon, nitrogen, and phosphorus—these have found expanding uses as "tracers" in biological systems. For the identification of intermediate compounds and the qualitative description of biochemical pathways and reaction mechanisms, they have allowed unprecedented advances; and some isotopically labeled substances also have been useful in analytical measurements—by the "isotope dilution" principle—of the quantities of material present or of their volumes of distribution in biological systems. A further type of use, of great potential importance theoretically, has often been attempted: by observation of the "movement" of labeled material to measure the absolute or relative *rate* of movement or of chemical transformation of unlabeled substance already present in the system. To the uninitiated in this field, this process would seem to be quite simple in principle. A substance containing a known quantity of the isotopic element would be introduced into the animal or surviving metabolizing system, and after a time one would find out how much of the isotope was present in a particular place or form. This might be feasible if one were dealing only with a single simple transfer of material from one "compartment" of known dimensions to another. In biological systems, however, this is very seldom the case. Instead, one finds that the transfer may be reversible; that what appears to be a simple transfer is in fact a series of reactions (some of them reversible, perhaps); that the substance introduced is itself being replaced with nonisotope material as fast as it is used; or that it can exchange with not one but many other forms. Hence the interpretation of rates of movement of the isotope in terms of the rates of movement of unlabeled materials is seldom simple and may be deceptively complicated.

By Jane A. Russell, from *Perspectives in Biology and Medicine*, Vol. 1, No. 2, Winter 1958.

Yeasts in Urine and Saliva of Diabetic and Nondiabetic Patients

Brigitte Mehnert, Ph.D., and Hellmut Mehnert, M.D., Boston

In recent years an increased incidence of fungus disease has been reported throughout the world.[1] It is likely that this development is particularly due to the introduction of broad spectrum antibiotics and is apparently a result of a temporary destruction of the harmless and useful bacterial flora which normally hold the fungus flora in check. However, certain primary diseases as diabetes mellitus seem able to favor per se the growth of various fungi, particularly in patients whose diabetes is poorly controlled.[2,3] In rabbits and mice in the acutely toxic state of alloxan diabetes, fulminating mucormycosis can be produced.[4,5] Moreover, it is a well-known fact that yeasts are seen frequently in urine sediments of diabetic patients and that there are sometimes diabetic patients with vaginitis due to Candida albicans ("Monilia"). Even a pyelitis due to Candida was recently seen in a diabetic patient in this clinic (case 2,568, female, aged forty-five, diabetes for thirty-six years). Finally, the skin of the diabetic appears to be more easily infected with Candida than that of the nondiabetic. After a primary incidence on the vulvar mucous membranes a possible later extension to the skin can occur.[6]

The present study was undertaken in an attempt to ascertain the incidence and types of living, potentially pathogenic yeasts in the urine and saliva of diabetic patients as compared with those of nondiabetics and to relate the incidence to the age and sex of patients, as well as to the presence or absence of glucosuria. It was hoped further to determine whether glucose utilization by yeasts could be of sufficient degree to produce a clinically significant decrease in the amount of sugar in the urine.

MATERIAL AND METHODS

Fresh urine specimens of 200 diabetic and 100 nondiabetic fasting patients were examined for the incidence of yeasts. Since there were fifty patients without glucosuria among the diabetics, a comparison was possible between 150 patients with glucosuria and 150 patients without glucosuria and between diabetics with and without glucosuria. In addition, the saliva of 160 diabetic and eighty nondiabetic fasting patients was examined for yeasts.

The culture of the yeasts was done by a recently described new method[7] enabling a selection of Candida species that may be pathogenic in man. By means of a relatively high acidity of the culture medium and cultivation at a temperature of 37° C., one can exclude the growth of nonpathogenic yeasts, occasionally occurring in the mouth, vagina, intestines and on the skin. Since the nonpathogenic yeasts are harmless saprophytes and are unable or only slightly able to grow within the human body, they are without importance for our investigation. Moreover, with this simple method one can avoid the usual time-consuming procedure of yeast identification which involves the use of up to thirty-eight different sugars and other compounds.

Using raw potatoes, boiled cold water, concentrated hydrochloric acid and concentrated lactic acid, two culture media were prepared for the differentiation of various Candida species. In one sterile Erlenmeyer flask were placed 100 cc. of water and 3 cc. of hydrochloric acid (assay: 37.2 per cent HCl). In the others were placed 100 cc. of water and 10 cc. of lactic acid (assay: 85 to 90 per cent $C_3H_6O_3$). To each flask were added raw potatoes, freshly peeled, washed and diced, in such quantity that the diced potatoes were covered by the liquid. The diced potatoes were kept in the flasks for two to three hours. The fluid was then decanted and the potatoes distributed to sterile test tubes filling up approximately one-third of each. To one-half of the test tubes, water and hydrochloric acid (*p*H 1-2), and to the other half, water and lactic acid (*p*H 3), were added so that fluid stood about 1 cm. over the potato substrate. Usually these test tubes, plugged with sterile cotton, can be used immediately. The high acid concentration prevents growth of bacteria and also avoids significant *p*H changes before

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the inoculation as well as during the cultivation at 37° C. However, to exclude any possibility of contamination, the test tubes were placed in an incubator at 37° C. before the inoculation in order to detect and eliminate any whose fluid showed turbidity in forty-eight hours.

In the examination of saliva for yeasts, a large drop of each sample was placed into each of two potato-containing test tubes, one containing hydrochloric acid, the other lactic acid. In the urine studies, 1.0 cc. and 0.1 cc. respectively of each specimen were in the same way put in the potato-containing test tubes, one with hydrochloric acid and the other with lactic acid. A microscopic examination of the sediment was done with all urine specimens for later comparison with the culture results. The incubated test tubes were checked macroscopically and microscopically after two days' incubation at 37° C. Growth of yeasts is macroscopically shown by a homogenous turbidity of the liquid medium as opposed to occasional flocculation due to saliva particles or lactic acid. Particular points regarding the identification of the yeasts can be seen in table 1. In cases of positive urine cultures, a "clean" voided specimen was obtained a few days later. With those specimens the same examination for yeasts was done.

To determine the glucose consumption of yeasts in urine containing glucose, 4 cc. of diabetic urine or normal urine (to which glucose was added in different concentrations) were inoculated with 1 cc. of a culture suspension (*p*H 3) of Candida albicans (density 97:3) in water and lactic acid. After twenty-four hours at room temperature, Benedict's test[8] and the di-nitro-salicylate method[9] were carried out both with these urine specimens and with control urine specimens, not inoculated with yeast.

RESULTS

No significant difference was found in the incidence of yeasts in the saliva of diabetics and that of nondiabetics. In almost one-half of all patients, yeasts—mostly Candida albicans—were found independent of the age and sex of the patients and the type or degree of diabetes (figure 1). Similar results in nondiabetics have been obtained by other workers.[10,11,12,13]

However, there was a clear-cut difference in the incidence of yeasts in the urine of diabetic and nondiabetic patients. On the other hand, this difference held only between nondiabetics and those diabetics with glucosuria (figures 2, 3 and 4). Patients with well-controlled dia-

TABLE 1

Growth of yeasts at 37° C.

Species		Evaluation of Growth	
		In potato substrate with hydrochloric acid (*p*H 1-2)	In potato substrate with lactic acid (*p*H 3)
Candida albicans*	Macroscopically:	Positive No film on the surface.	Positive No film on the surface. Only a ring appears.
	Microscopically:	Round or short oval budding cells occurring singly, in pairs or clusters. Usually a pseudomycelium is produced.	
Candida krusei	Macroscopically:	No growth	Positive A thin, dull, creeping film is formed on the surface.
	Microscopically:	———	Usually elongate or less commonly, short oval cells occur singly, in pairs or chains. Occasionally pseudomycelium is produced.
Candida tropicalis	Macroscopically:	No growth	Positive
Candida pseudotropicalis			No film on the surface. Occasionally a ring is observed.
Candida utilis			
Candida parapsilosis			
	Microscopically:	———	Short oval to oval budding cells, mostly in clusters. Sometimes pseudomycelium.

* Torulopsis glabrata also grows in HCl. However, it does not form a pseudomycelium and shows a smaller size of cells. This species was not found in the present study.

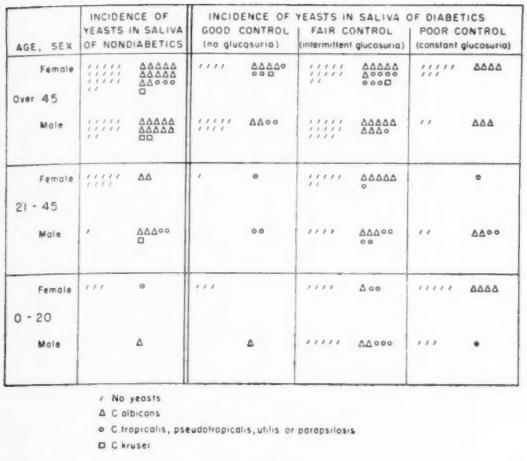

FIG. 1. Incidence of yeasts in saliva.

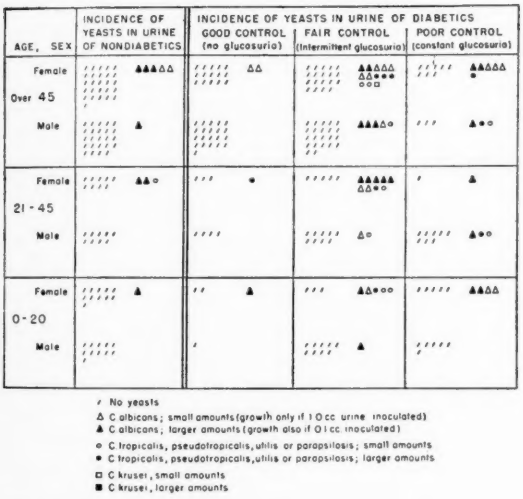
AGE, SEX
INCIDENCE OF YEASTS IN URINE OF NONDIABETICS
INCIDENCE OF YEASTS IN URINE OF DIABETICS
GOOD CONTROL (no glucosuria)
FAIR CONTROL (intermittent glucosuria)
POOR CONTROL (constant glucosuria)
Female
Over 45
Male
Female
21 - 45
Male
Female
0 - 20
Male
No yeasts
C albicans; small amounts (growth only if 1.0 cc urine inoculated)
C albicans; larger amounts (growth also if 0.1 cc inoculated)
C tropicalis, pseudotropicalis, utilis or parapsilosis; small amounts
C tropicalis, pseudotropicalis, utilis or parapsilosis; larger amounts
C krusei, small amounts
C krusei, larger amounts

FIG. 2. Incidence of yeasts in urine.

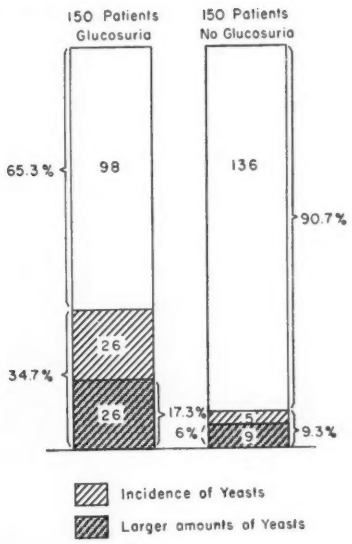

FIG. 3. Incidence of yeasts in urine of patients with glucosuria and without glucosuria.

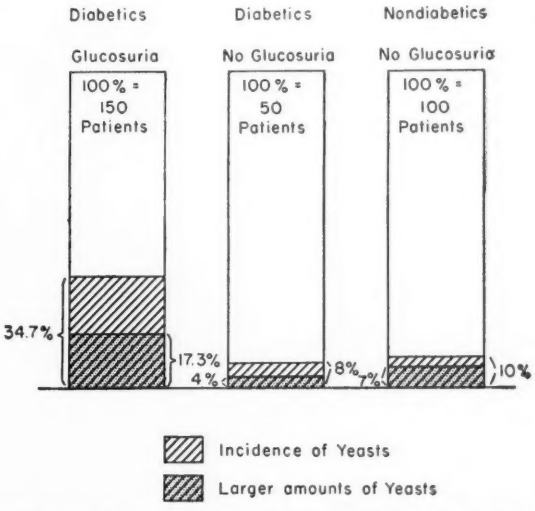

FIG. 4. Incidence of yeasts in urine of diabetics with glucosuria and diabetics and nondiabetics without glucosuria.

betes and without glucosuria showed the same incidence of yeasts as nondiabetics and only one-fourth that of patients with glucosuria (figure 4). All yeasts isolated were species of Candida ("Monilia"), preponderantly Candida albicans (figure 2). There was no difference in the incidence of yeasts in diabetics with "fair" control (intermittent glucosuria) and those with "poor" control (constant glucosuria) (figure 2). Apparently the deciding factor favoring the growth of yeasts in urine is glucose alone, independent of its amount. There was also no significant difference in the various age groups. However, female diabetic and nondiabetic patients showed yeasts in a distinctly higher percentage than male patients, both diabetic and nondiabetic (figure 5). Examination of "clean" voided specimens (figure 6) yielded confirmation of our results in approximately 80 per cent. Therefore, one may suppose in these cases that yeasts occurred in the bladder as well as in the external urogenital tract. However, using the common

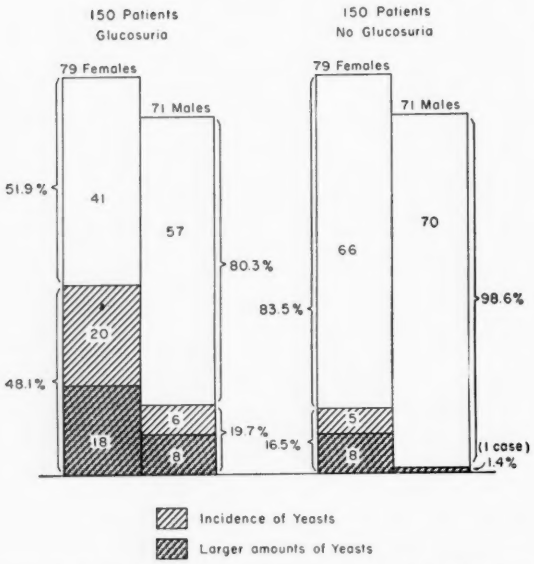

FIG. 5. Incidence of yeasts in the urine of female and male patients with and without glucosuria.

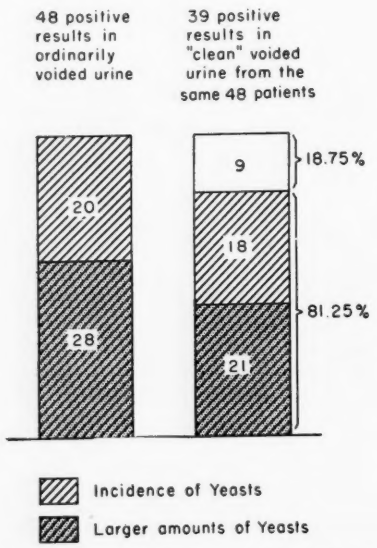

FIG. 6. Diabetic and nondiabetic urine (ordinarily voided) containing yeasts compared with "clean" voided specimens of the same patients.

microscopical examination of urine sediment, yeasts were recognized in only 10 per cent of the urine specimens which were later shown on culture to contain yeasts. This finding shows the possibility of overlooking yeasts by microscopic examination alone and demonstrates the sensitivity of the culture method used. Among patients in whom no growth of yeasts occurred in the potato substrate, there was no instance in which yeasts were seen in the urine sediment on microscopic examination.

TABLE 2

Effect of 24-hour growth of Candida albicans on concentration of glucose in urine

Case	Control urine not inoculated Glucose, per cent	Urine inoculated with Candida Glucose, per cent
1	1.0	0.6
2	1.9	1.4
3	3.4	2.8
4	3.0	2.6
5	0.6	0.5

The di-nitro-salicylate method (Sumner and Exton) was used. In each case the urine originally contained no yeasts. Starting the test, yeasts were inoculated into one-half of every specimen. These results were confirmed by the Benedict's test (no change was shown in the glucose concentration in Case 5).

As may be seen in table 2, even at room temperature, Candida may cause a significant loss of glucose from urine. Although the addition of toluene (5 cc. to 2 liters of urine) suppresses the growth of bacteria, it does not prevent the growth of yeasts in urine collected in a large bottle over a twenty-four-hour period at room temperature.

DISCUSSION

The present study has shown that yeasts are found much more frequently in urine containing glucose, especially in female patients. It is well known that bacterial urogenital infection is also more common in women than in men, due chiefly to Escherichia coli from the feces. The gastrointestinal tract is a reservoir for Candida as well.[14] Since yeasts prefer to grow on mucous membranes (e.g., those of the vagina), there seem to be two reasons for the greater incidence of yeasts in the urine of female persons: (1) easier infection of the urogenital tract with yeasts from feces, and (2) favorable conditions for growth of yeasts in the vagina. In diabetic women with glucosuria a third and probably most important factor for better growth is present: glucose in the urine.

With certain types of Candida found in the human body, the degree of fungus concentration is related to pathogenicity.[15] Therefore, in diabetic patients the treatment of vaginitis or other urogenital infections due to Candida requires a rigid control with complete lack of

glucose in the urine as the primary feature of therapy. One cannot expect success from local treatment of vaginitis as long as growth of yeasts continues in the bladder urine. Furthermore, a logical assumption would be to expect an increased incidence of Candida and greater danger of fungus infection in patients with glucosuria who are receiving antibiotics. Therefore, strict attention should be given to the attainment of a sugar-free urine in these patients as well.

Occasionally the glucose consumption by Candida in diabetic urines can amount to several grams within twenty-four hours and can lead to an undervaluation of the real glucose excretion in urine collected by the patient for one day. A report regarding substances able to prevent growth of yeasts in such urine will be made later.

SUMMARY

1. Urine specimens of 200 diabetic and 100 nondiabetic persons as well as the saliva of 160 diabetic and 80 nondiabetic individuals were examined for the incidence of those yeasts which are potentially pathogenic in men. A new method of identification was used.

2. Almost half of the diabetic and nondiabetic patients showed yeasts in the saliva without any significant differences between the two groups.

3. The incidence of yeasts in the urine of patients with glucosuria was almost four times that in patients without glucosuria without regard to whether the patients without glucosuria were nondiabetics or patients with well-controlled diabetes. Furthermore, yeasts occurred in the urine of diabetic and nondiabetic female patients much more commonly than in male patients.

4. The growth of Candida species in glucose-containing urine kept at room temperature reduced the concentration of glucose.

SUMMARIO IN INTERLINGUA

Saccharomycetes In Le Urina De Patientes Diabetic E Nondiabetic

1. Specimens de urina ab 200 diabeticos e 100 nondiabeticos e specimens de saliva ab 160 diabeticos e ab octanta nondiabeticos esseva examinate pro le incidentia del typos de saccharomycete que es potentialmente pathogene in humanos. Un nove methodo de identification esseva usate.

2. Quasi un medietate del diabeticos e del nondiabeticos habeva saccharomycetes in lor saliva. Le differentia inter le duo gruppos non esseva significative.

3. Le incidentia de saccharomycetes in le urina de patientes con glucosuria esseva quasi quatro vices illo in le urina de patientes sin glucosuria, sin reguardo a si le patientes sin glucosuria esseva nondiabeticos o patientes con diabete de forma ben regulate. In plus, saccharomycetes occurreva in le urina de patientes diabetic e nondiabetic de sexo feminin multo plus communmente que in patientes de sexo mascule.

4. Le crescentia de species de Candida in urina a contento de glucosa, quando mantenite al temperatura normal de interior, reduceva le concentration de glucosa.

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Diabetes Following Total Pancreatectomy

Clinical Observations of Ten Cases

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More than seventy years ago Billroth[1] claimed to have performed the first successful total pancreatectomy in man, and sixteen years later Franke[1] reported that he also had successfully performed that operation. No details are available of Billroth's case, except that the patient recovered. In Franke's patient a small mass of pancreatic tissue remained which was thought to represent a supernumerary pancreas. The patient recovered. It seems obvious that total pancreatectomy was not performed in either of these instances, because they predate the discovery of insulin in 1921, and its administration is essential for survival after that operation. In man[2] and in dogs[3] more than 90 per cent of the pancreas must be removed to induce a diabetic state.

In normal adults the pancreas weighs from 60 to 160 gm. (average, approximately 95 gm.), and may contain between 208,000 and 2,500,000 islets based on estimations made with the new staining and counting technics. The islets represent between 1.0 and 3.5 per cent of the total pancreas.[4] Insulin content in a normal person is estimated to be 1.7 units per gm. of pancreatic tissue;[5] in a diabetic person it is estimated to be about 0.4 units per gm., although even normal concentrations have been found in persons with severe diabetes. Wrenshall and associates[6] found that the insulin in the pancreas of nondiabetics ranged from 1.3 to 3.5 units per gm. of pancreatic tissue, while in diabetics the values ranged from 0.2 to 1.4 units per gm. They believe that "insulin extractable from the pancreas" is a more appropriate term than "insulin content," because there is no proof that the insulin determinations at any particular moment actually represent the total amount of insulin within the pancreas. It is believed that normal pancreatic tissue has a large functional capacity and is capable of producing at least 30 units of insulin per day.[7] Ricketts and associates[8] reported the effects of total pancreatectomy in one diabetic patient who before operation required from 40 to 80 units of insulin daily, and after operation required an average of 40 units of insulin daily. According to Gaston,[9] the first seven patients who survived total pancreatectomy required an average of 42 units of insulin daily.

The first successful total pancreatectomy was reported by Priestley[2] in 1942 and since that time there have been twenty-nine additional reports of patients who underwent this operation and survived the immediately postoperative period.[10]

This report discusses postpancreatectomy problems in nutrition and in diabetic control in patients whose conditions included the presence of carcinoma.

MATERIALS AND METHODS

The series comprises ten patients with carcinoma (table 1) treated by total pancreatectomy. Three patients had diabetes which was discovered immediately before operation and was well controlled at the time of operation. No insulin was given preoperatively to one of these patients. In the other seven patients diabetes became evident after operation.

Blood sugar determinations commonly were made from one to three times daily; urinalysis was performed every two to four hours in the early postoperative period. At first the blood sugar was measured fasting and usually three hours postprandially daily, but later the tests were done every few days. Urine sugar was estimated before each meal and at bedtime. The blood sugar tests were done by a modification of the Myers-Bailey method and the urine sugar tests were qualitative Benedict tests.

Whenever possible, all insulin was administered before breakfast. During the early postoperative period regular insulin, in variable doses, was given several times a day in an attempt to control glycosuria. To each liter of 5 per cent dextrose administered, 10 to 25 units of regular insulin was added.

It is our practice to attempt to control diabetes mellitus in such a way as to maintain weight and strength, to avoid ketosis and glycosuria, and, so far as possible, to keep blood sugar values within normal range at all times of day. It soon became apparent in treating patients after pancreatectomy that such ideal control could not be even closely approximated. Diarrhea often aggravated the decrease in food absorption typical of the lack of pancreatic enzymes, and there were serious barriers

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TABLE 1

Status in relation to primary pathology

Case No.	Pathologic Condition	Postoperative Survival Period	Primary Cause of Death
1	Adenocarcinoma of common bile duct and pancreas	7 mo.	Septicemia; secondary carcinoma of liver
2	Adenocarcinoma of pancreas	5½ mo.	Metastatic carcinoma*
3	Adenocarcinoma of the ampulla of Vater	30 mo.	Died at home after being comatose 4 days; cause not determined*
4	Adenocarcinoma of pancreas and papillary carcinoma of bladder	2 mo.	Insulin-induced hypoglycemia
5	Adenocarcinoma of pancreas and common bile duct	9 mo.	Metastatic carcinoma?*
6	Carcinoma of duodenum	4 yr.	Not known
7	Adenocarcinoma of pancreas	23 mo.	Metastatic carcinoma?* (Died at home)
8	Adenocarcinoma of pancreas	4 mo.	Metastatic carcinoma*
9	Carcinoid of ampulla of Vater	4 yr. (living)	—
10	Adenocarcinoma of pancreas	14 mo.	Metastatic carcinoma

*No necropsy performed.

to the maintenance of normal nutrition despite a high caloric intake in some patients. Insulin sensitivity was a striking feature and, because of the extreme severity of insulin reactions, it was decided that short-acting insulin was safer to use than long-acting insulin, and that slight hyperglycemia was preferable to risking the danger of fatal insulin reactions.

CASE REPORTS

Case 1. A fifty-four-year-old white woman was first seen in 1952, because of severe, cramping, nonradiating pain in the right upper quadrant of the abdomen; it occurred about twice weekly during the preceding three or four months. She obviously was jaundiced. A blood count was normal. The preoperative fasting blood sugar value was 316 mg. per 100 ml. with 4 plus glycosuria. Serum bilirubin was 14.5 mg. per 100 ml. (direct) and 9.3 mg. per 100 ml. (indirect); total serum protein, 7.1 gm. per 100 ml.; serum albumin, 3.1 gm. per 100 ml.; serum globulin, 4.0 gm. per 100 ml.; thymol turbidity, 3.9 units; cephalin-cholesterol flocculation, negative in 24 hr.; prothrombin time, 14 sec.; serum alkaline phosphatase, 42.6 Bodansky units.

Preoperatively, the diabetes was controlled by a diet of 1,840 calories and 45 units of NPH insulin* given daily before breakfast. On the morning of the day of operation only 20 units of NPH insulin was administered. At operation an adenocarcinoma of the common bile duct with extension into the head of the pancreas was found; the liver was enlarged with the gross appearance of biliary cirrhosis. A total pancreatectomy was performed.

The patient did well during the immediately postoperative period. During the first four days, 30 units of NPH insulin was given at 7 a.m. and regular insulin from 12 to 30 units once or twice daily during periods of "4 plus" glycosuria. To each liter of 5 per cent dextrose was added 15 or 30 units of regular insulin.† The blood sugar values ranged from 50 to 275 mg. per 100 ml. On the sixth postoperative day an insulin reaction occurred. On the sixteenth postoperative day the patient was discharged from the hospital and was advised to take 10 units NPH insulin daily, a 1,712-calorie diet (CHO:200;P:120;F:48) and pancreatic extract* 120 grains daily. However, there was a gradual loss of 15 lb. in weight, and occasionally, during the next few weeks, loose, foul-smelling stools were discharged four or five times daily. The latter condition was partially relieved by the use of another preparation of pancreatic extract (Viokase)† in a dosage of three tablets three times daily with meals. Her appetite improved; the total daily dietary intake was increased to 1,952 calories with 240 gm. of carbohydrate, and the daily requirement of NPH insulin increased from 10 to 30 units.

Approximately seven months after operation, the patient was readmitted to the hospital because of anorexia and alternating chills and fever of two weeks' duration. Physical examination revealed a tender, hard, stony mass in the right upper quadrant of the abdomen. A laparotomy was performed to obtain a biopsy specimen; the report showed the mass to be identical with the original lesion. During the next six days the patient's condition worsened; staphylococcal septicemia with septic emboli developed as did abscesses of the hands and feet. However, the insulin requirement remained the same until three days prior to her death, when it decreased to 10 units of NPH. She died seven months after pancreatectomy.

Case 2. A sixty-three-year-old white woman was first seen in 1953 because of progressive jaundice, nausea, and loss in weight which had occurred during the preceding thirty days. Physical examination disclosed no other abnormalities. A blood count and urinalysis were normal. Total serum protein was 7.8 gm. per 100 ml.; serum albumin, 4.9 gm. per 100 ml.; serum globulin, 2.9 gm. per 100 ml.; serum alkaline phosphatase,

*NPH Iletin Insulin—Neutral Protamine of Hagedorn Insulin (Eli Lilly & Company, Indianapolis).

†Regular insulin—amorphous Iletin Insulin (Lilly).

*Pancreatic extract—Pancreatin—Panteric Tablet—5 grain, Triple U.S.P. strength (Parke, Davis, & Co., Detroit)—product derived from fresh hog or cattle pancreatic tissue containing enzyme amylase, trypsin, and lipase.

†Viokase Tablet—5 grain (Viobin Corp.)—product consisting of activated, desiccated, and defatted whole raw pancreas. It is 4 x U.S.P. strength of pancreatin.

15.5 Bodansky units; icterus index, 80; serum bilirubin, 9.0 mg. per 100 ml. (direct) and 5.7 mg. per 100 ml. (indirect). Thymol turbidity was 1.8 units, and cephalin-cholesterol flocculation was negative in twenty-four hours. At operation, an adenocarcinoma, limited to the head of the pancreas, was found. The elective procedure was total pancreatectomy. The liver appeared normal.

The postoperative course was complicated by bile peritonitis and cystitis. From 32 to 90 units of regular insulin was given in fractional doses (table 2). About one month postoperatively, the insulin requirement ranged from 20 to 30 units of NPH insulin but the prescribed diet had not been followed. The food intake approximated 190 gm. carbohydrate with 1,100 calories daily. Two months after operation the insulin requirement had increased to 38 units of NPH and 16 units of regular insulin (mixed and administered before breakfast), while the food intake averaged 175 gm. carbohydrate and 1,400 calories daily, with the blood sugar maintained at fairly normal levels. The insulin requirement later dropped to 10 units of NPH with blood sugar values of 155 mg. per 100 ml. three hours postprandially and 59 mg. per 100 ml. fasting. This was shortly followed by two severe insulin reactions, each of which responded to 50 gm. of dextrose given intravenously. It is likely that the sudden change in insulin requirement was provoked by concurrent improvement in the urinary tract infection.

Two days after the insulin reactions, a cerebral accident occurred resulting in left hemiparesis. The blood sugar ranged from 200 to 500 mg. per 100 ml. During the succeeding forty-five days, manifestations in the central nervous system improved; the dietary intake increased to 2,038 calories (CHO: 181;P:99;F:102) and the insulin requirement increased to 30 units of NPH.

The development of Jacksonian epilepsy, which was controlled by Dilantin* (1½ grains four times daily), suggested the possibility of cerebral metastatic lesions, although there was no direct evidence that this was the only factor causing the symptoms in the central nervous system. During the five postoperative months that the patient was in the hospital, she refused to take pancreatic extract, but there was no diarrhea.

Two weeks after discharge, the patient was readmitted to the hospital in a semicomatose state; she died six days later. Necropsy was not performed. The patient survived five and one-half months after total pancreatectomy.

Case 3. A fifty-eight-year-old white woman was first seen in April, 1953, after three weeks of progressive and painless jaundice, pruritis, constipation, and anorexia. On physical examination, icterus was the only significant finding. A blood count, urinalysis, blood urea, blood Wassermann and Kahn tests were normal. A fasting preoperative blood sugar value was 87 mg. per 100 ml. Total serum protein was 6.2 gm. per 100 ml.;

*Dilantin Sodium Kapseals (Parke-Davis)—anticonvulsant containing diphenylhydantoin sodium.

TABLE 2

Case 2. Postoperative course pertaining to control of diabetes mellitus (total pancreatectomy)

Days Postop.	Time	Insulin (Units)	Laboratory Determinations: Blood Sugar mg./100 ml.	Urine Sugar	Acetone	Intake*
1	9 a.m.	6 Reg.	366	++++	+	2,000 cc. 5% dextrose solution and saline
	11 a.m.	6 Reg.		++++	0	IV with 30 units of regular insulin
	4 p.m.	10 Reg.		++++	0	
	11 p.m.	10 Reg.		++++	0	
2	2 a.m.	7 Reg.	222	+++		Intake*
	6 a.m.	7 Reg.		++++	0	2,000 cc. 5% dextrose solution and saline
	12 noon	None		++++	0	IV with 30 units of regular insulin
	4 p.m.	10 Reg.		++++	0	
	9 p.m.	10 Reg.		++++	0	
3	7 a.m.	10 Reg.		++++	0	2,000 cc. 5% dextrose solution and saline
	12 noon	5 Reg.	150	++	0	IV with 30 units of regular insulin
	4 p.m.	7 Reg.	270	+++	0	
	8 p.m.	7 Reg.		+++	0	
5	7 a.m.	17 Reg.	158	+++	0	CHO:174;P:73;F:51; calories 1,447 orally.
	12 noon	None		No spec.	0	Patient could not be aroused at 7 a.m.—
	4 p.m.	5 Reg.	340	++	0	he responded after 100 gm. carbohydrate.
	11 p.m.	6 Reg.		+++	0	
11	7 a.m.	10 Reg.	333	++++	0	3,000 cc. 5% dextrose solution given with
	12 noon	8 Reg.		++++		saline IV with 45 units of regular insulin
	4 p.m.	10 Reg.		No spec.		
	11 p.m.	16 Reg.		++++		
25	7 a.m.	24 NPH	300	+++	0	CHO:160;P:98;F:50; calories 1,484, or-
	11 a.m.	None		No spec.		ally
	4 p.m.	8 Reg.		++++	0	
	11 p.m.	None		+++	0	

*Diabetic diet prepared for jejunostomy feedings, consisting of milk, water, and 5% dextrose in water mixture, was administered on various occasions.

serum albumin, 3.3 gm. per 100 ml.; serum globulin, 2.9 gm. per 100 ml.; thymol turbidity, 1.1 units; cephalin-cholesterol flocculation, negative in 24 hr.; serum bilirubin, 3.7 mg. per 100 ml. (direct) and 3.2 mg. per 100 ml. (indirect).

Total pancreatectomy was performed for a grade III differentiated adenocarcinoma of the ampulla of Vater with invasion of the head of the pancreas. The liver was apparently normal.

The postoperative course was highly satisfactory. For six days, the diabetes was extremely benign with blood sugar values ranging from 83 to 190 mg. per 100 ml. and with only 1 to 2 plus glycosuria. Twelve units of NPH insulin was administered before breakfast each morning. To each liter of 5 per cent dextrose, 15 units of regular insulin was added during this time. On the twenty-sixth postoperative day she was discharged. Her regimen consisted of 10 units of NPH insulin daily, an 1,884-calorie diet (CHO:205;P:86;F:80), choline dihydrogen citrate tablets 10 grains three times daily, Becotin* capsule one twice daily, Bilron† capsule one twice daily, and pancreatic extract tablets 15 grains three times daily. Supplementary protein feedings (eggnog, Sustagen§ feedings) were advised, but it is doubtful that they were taken. She experienced no diarrhea or gross steatorrhea. When she was seen fifteen months after the operation, there were no findings suggestive of recurrent or metastatic lesions; her general condition and nutritional status remained satisfactory, except for a 20-lb. loss in weight. Twenty-six months postoperatively she returned because of pain and a tender mass in the right upper quadrant. A laparotomy was performed and a recurrent carcinoma of the abdominal wall was found; again the liver appeared normal. Four months later (thirty months postoperatively) the patient died at home after being comatose for a four-day period. Necropsy was not performed.

Case 4. A fifty-five-year-old white man was first seen in April, 1950, after seven weeks of intermittent jaundice, severe burning epigastric pain, and a loss in weight totaling 47 lb. Physical examination revealed a markedly icteric patient in no acute distress. A blood count, urinalysis, blood urea and blood Wassermann and Kahn tests were normal. A preoperative fasting blood sugar value was 139 mg. per 100 ml. There were no other blood sugar determinations, but this single value was considered to denote diabetes mellitus. No preoperative insulin was administered. Total serum protein was 7.2 gm., with serum albumin 3.6 gm., and serum globulin 3.6 gm.; prothrombin time, 14 sec. (100 per cent); and serum bilirubin 34 mg. per 100 ml. (direct). Thymol turbidity was 1.1 units and cephalin-cholesterol flocculation was negative in twenty-four hours. At operation, an adenocarcinoma of the pancreas was diagnosed and a total pancreatectomy was performed. The immediately postoperative course was uneventful, requiring variable doses of insulin as noted in table 3. On the sixth postoperative day hypoglycemia developed and persisted for five days (table 3). During this period insulin was administered each morning for three consecutive days. Following an insulin reaction, the dosage was decreased on the third day; subsequently no insulin was administered for a period of three days with hypoglycemia persisting in the absence of insulin for two days and absent glycosuria for an additional day. During this period the food intake averaged 160 gm. of carbohydrate and 1,700 calories daily. The prolonged hypoglycemia and absent glycosuria can best be explained by an excessive and accumulative dose of Protamine Zinc insulin.*

On the twenty-second postoperative day the patient was discharged and was advised to follow an 1,827-calorie diet (CHO: 160;P:74;F:99) and to take 15 units of Protamine Zinc insulin (PZI) and 15 units of regular insulin (given separately before breakfast). Approximately one and one-half months after discharge the patient returned to the hospital because of gross hematuria. A grade III papillary transitional-cell carcinoma of the bladder was discovered to be the cause of the hematuria. The fasting blood sugar value on the morning of operation was 57 mg. per 100 ml., and 15 units of PZI was administered. During transurethral resection, 22 units of regular insulin was given in approximately 850 cc. of 5 per cent dextrose in water and saline solution. About ten hours postoperatively, the patient went into shock and did not respond to whole-blood transfusions and intravenous fluids containing a total of 100 gm. of carbohydrate. Despite the administration of an additional 200 cc. of 50 per cent dextrose intravenously, the general picture of shock and mental confusion did not change. Unfortunately no further blood sugar determinations were made. The patient died approximately eighteen hours after operation. Necropsy was not permitted. The patient had survived two months after the total pancreatectomy.

Case 5. A fifty-four-year-old Negro man was first seen in 1949 because of lower abdominal cramping pain that had been occurring about thirty minutes after each meal for three weeks. The only pertinent physical findings were jaundice and a palpable gall bladder. A blood count and urinalysis were normal. A preoperative fasting blood sugar value was 98 mg. per 100 ml.; serum amylase, 412 units; serum bilirubin, 12.1 (direct); cephalin-cholesterol flocculation, negative in twenty-four hours; thymol turbidity, 0.7; and prothrombin time, 17 sec. (72 per cent). A total pancreatectomy was performed for a moderately differentiated adenocarcinoma of the head of the pancreas with invasion of the common bile duct. The liver was slightly enlarged secondary to bile stasis. During the first four postoperative days the insulin doses ranged from 30 to 40 units of PZI before breakfast, and from 20 to 30 units of regular insulin throughout the day to correct glycosuria; additional regular insulin in doses of 20 units was added to each liter of 5 per cent dextrose. The glycosuria ranged between 2 plus and 4 plus on tests made every two to four hours. Blood sugar values ranged from 47 to 511 mg. per 100 ml. without incident.

On the fourteenth postoperative day the patient was discharged and was advised to follow a 2,600-calorie diet (CHO: 250;P:120;F:140) and to take a mixture of 15 units PZI with 15 units of regular insulin before breakfast daily. About two months later, the insulin dosage was decreased to 10 units of PZI and 10 units of regular insulin because of an occasional mild insulin reaction. There was an average of one bulky, yel-

*Becotin (Lilly)—vitamin B complex capsule consisting of thiamine HCl, riboflavin, pantothenic acid, Vitamin B_{12}, pyridoxine HCl, nicotinamide, desiccated liver and stomach tissue material.

†Bilron (Lilly)—5-grain capsule containing a compound of iron and bile acids.

§Sustagen (Mead Johnson & Co., Evansville, Ind.)—nutritional product consisting of protein 23.5 per cent, carbohydrates 66.5 per cent, and fat 3.5 per cent, iron, calcium, and vitamins.

*Protamine Zinc Insulin (Lilly).

TABLE 3

Case 4. Postoperative course pertaining to control of diabetes mellitus (total pancreatectomy)

Days Postop.	Time	Insulin (Units)	Laboratory Determinations: Blood Sugar mg./100 ml.	Urine Sugar	Acetone	Intake
1	2 p.m.	15 PZI*	384	+	0	3,000 cc. 10% dextrose solution with 90 U. regular insulin
	4 p.m.			+++	0	
	8 p.m.			++++	0	
	10 p.m.	8 Reg.				
2	10 a.m.	25 PZI	169	+++	0	3,000 cc. 10% dextrose solution with 90 U. regular insulin
	5 p.m.	5 Reg.		+++	0	
	11 p.m.			+++	0	
3	7 a.m.		240	+	0	2,000 cc. 10% dextrose solution with 60 U. regular insulin
	2 p.m.	35 PZI 15 Reg.		0	0	
	5 p.m.	8 Reg.	219	++++	0	
	11 p.m.			+	0	
6	8 a.m.	40 PZI	57	0	0	2,000 cc. 10% dextrose solution with 60 U. regular insulin; 50 cc. 50% dextrose solution for insulin reaction
	11 a.m.		39	+	0	
	5 p.m.	8 Reg.		++++	0	
	11 p.m.			+	0	
7	8 a.m.	40 PZI	32	trace	0	Total—not recorded. 50 cc. 50% dextrose solution
	11 a.m.		32	trace	0	
	5 p.m.		32	trace	0	
	11 p.m.			trace	0	
8	8 a.m.	30 PZI	28	0	0	100 cc. 50% dextrose solution
	11 a.m.		35	0	0	CHO:170;P:59;F:96; 1,780 calories orally
	5 p.m.		35	0	0	
	11 p.m.			0	0	
9	8 a.m.	0	35	0	0	CHO:170;P:59;F:96; calories 1,780 orally
	11 a.m.		21	0	0	
	4 p.m.			0	0	
	11 p.m.			0	0	
10	8 a.m.	0	32	0	0	CHO:167;P:63;F:93; calories 1,757 orally
	11 a.m.		50	0	0	
	4 p.m.		83	0	0	
	11 p.m.			trace	0	
11	8 a.m.	0	147	0	0	CHO:175;P:61;F:81; calories 1,665 orally
	11 a.m.			0	0	
	4 p.m.			0	0	
	11 p.m.			0	0	
12	8 a.m.	4 Reg.		+++	0	CHO:163;P:69;F:91; calories 1,747 orally
	11 a.m.	2 Reg.		++	0	
	4 p.m.			0	0	
	11 p.m.			++	0	
13	8 a.m.		380	++++	0	CHO:160;P:72;F:99; calories 1,817 orally
	11 a.m.		394	0	0	
	4 p.m.	10 Reg.	454	++++	0	
	11 p.m.			+	0	
14	10 a.m.	30 Reg.	423	+	0	CHO:162;P:71;F:90; calories 1,742 orally
	1 p.m.	8 Reg.	240	++++	++++	
	3 p.m.	50 Reg.		+++	+++	
	8 p.m.				0	
17	8 a.m.	15 Reg.	297	0	0	CHO:162;P:73;F:90; calories 1,750 orally
	11 a.m.		214	0	0	
	5 p.m.	15 Reg.		+++	0	
	11 p.m.			0	0	

*Protamine Zinc Insulin.

low, foul-smelling stool daily until pancreatin tablets (90 grains daily) had been taken for about one month postoperatively. Seven months postoperatively, some personality changes developed in the patient while at home, with periods of weakness and night sweats that were partially improved when the patient drank orange juice. He still was receiving a 2,600-calorie diet and taking a mixture of 10 units of PZI and 10 units of regular insulin. One month later mental confusion developed and was followed by unconsciousness. He was seen terminally when the blood sugar value was 40 mg. per 100 ml. After a total of 250 gm. of dextrose had been given intravenously during a six-hour period, the blood sugar value was 220 mg. per 100 ml. His clinical status failed to change. About twelve hours later, the blood sugar value was 44 mg. per 100 ml., although no further insulin had been administered. After the additional administration of 225 gm. of dextrose intravenously during a twelve-hour period, the blood sugar value became elevated to 394 mg. per 100 ml. and the patient's mental status improved. Despite the maintenance of blood sugar values of about 200 to 300 mg. per 100 ml., he continued to have episodes of excessive perspiration which subsided after the drinking of orange juice. Neurologic findings were not suggestive of a focal lesion. During the following few days, the blood sugar values decreased from 200 to 300 mg. per 100 ml. to 70 to 160 mg. per 100 ml., although no insulin was administered. The patient gradually lapsed into a state of mental confusion and lethargy and subsequently died. Because of the development of hepatomegaly and concomitant mental changes that remained unaltered despite the correction of the hypoglycemia, the patient's death was attributed to hepatic and cerebral metastatic carcinoma. Necropsy was not permitted. The patient had survived nine months after total pancreatectomy.

Case 6. A forty-two-year-old white woman was seen in June, 1953, because of epigastric pain of two months' duration which was relieved by food or alkali. Findings on systemic review and physical examination were normal. A blood count was normal. Urinalysis was negative except for a few pus cells. A preoperative fasting blood sugar value was 96 mg. per 100 ml. Liver function tests were not performed. Total pancreatectomy was performed for an adenocarcinoma of the third portion of the duodenum. The liver appeared normal. During the first four postoperative days the requirement was about 8 units of regular insulin every four to six hours and 15 units of PZI before breakfast or lunch to maintain fasting blood sugar values from 200 to 300 mg. per 100 ml. To each liter of 5 per cent dextrose given during this postoperative period, 15 units of regular insulin was added. Until time of discharge the insulin requirement was from 10 to 15 units of PZI daily. Blood sugar values ranged from 150 to 250 mg. per 100 ml. throughout the day. On the fourteenth postoperative day she was discharged and was instructed to follow a 1,400-calorie diet (CHO:145;P:71;F:60) and to take 20 units of PZI daily.

Three months later her condition was found to be satisfactory. She had lost 12 lb. but the diabetes had been well controlled as reflected by a fasting blood sugar of 149 mg. per 100 ml. The diet was increased to 2,052 calories (CHO:205; P:83;F:100) and the insulin to 28 units NPH. At the time of her last examination, twelve months after total pancreatectomy, she had gained 20 lb. in weight; her progress and general condition at the time were again satisfactory.

It is interesting to note that although this patient took no pancreatic extract, she experienced no postoperative abdominal cramps and had no diarrhea. She did not return for a progress examination. The patient died four years following surgery. The course and mode of death are unknown to us.

Case 7. A sixty-year-old white woman was first seen in January, 1954, because of intermittent pain in the right upper quadrant of the abdomen and midepigastric gnawing pain with progressive jaundice of four weeks' duration. Physical examination revealed an icteric woman in no apparent distress. A blood count, urinalysis, blood urea, and blood Wassermann and Kahn tests were normal. A fasting preoperative blood sugar value was 101 mg. per 100 ml. Total serum protein was 7.2 gm. per 100 ml., with serum albumin 3.9 gm. per 100 ml. and serum globulin 3.3 gm. per 100 ml.; prothrombin time was 100 per cent; serum bilirubin, 5.1 mg. per 100 ml. (direct) and 7.2 mg. per 100 ml. (indirect); cephalin-cholesterol flocculation, 4 plus in 24 hr. Thymol turbidity was 0.5 units; alkaline phosphatase, 12.7 Bodansky units; serum amylase, 163 units. At the time of abdominal exploration a total pancreatectomy for adenocarcinoma of the pancreas was performed. No grossly abnormal hepatic findings were noted.

During the first six postoperative days 10 units of regular insulin was given at 7 a.m. daily. To each liter of 5 per cent dextrose 10 units of regular insulin was added during this time. Blood sugar values ranged from 160 to 375 mg. per 100 ml. Between the seventeenth and twenty-fifth postoperative days the blood sugar values ranged from 110 to 150 mg. per 100 ml. fasting, and 165 to 275 mg. per 100 ml. at 4 p.m., with a carbohydrate intake of 160 gm. and a caloric intake ranging from 1,364 to 1,450 daily.

For reasons not apparent to us now, the physician in charge prescribed corticotropin (ACTH) 10 units intramuscularly daily from the first to the sixth postoperative days inclusive, and cortisone 50 mg. intramuscularly daily from the second to the fifth postoperative days inclusive. It is of interest that in this period the patient's insulin requirements were not significantly different from those of others receiving no steroids.

The postoperative course was relatively uneventful. On the twenty-ninth postoperative day the patient was discharged and was advised to follow a diet containing 1,637 calories (CHO: 180;P:83;F:65) with 18 units of NPH insulin daily. One month later her general condition was found to be satisfactory except for a weight loss of 16 lb. She averaged three or four well-formed stools each day, and there appeared to be no need for pancreatic extract. Six months postoperatively, while the patient was taking 200 gm. of carbohydrate and 1,870 calories daily, and 20 to 24 units of regular insulin after breakfast and 4 to 8 units after the evening meal, the blood sugar values ranged from 80 to 200 mg. per 100 ml. fasting, from 130 to 350 mg. per 100 ml. three hours after breakfast, and from 95 to 575 mg. per 100 ml. three hours after the noon meal.

Seventeen months later (twenty-three months postoperatively) the patient died at home. Necropsy was not permitted.

Case 8. A sixty-two-year-old white man was first seen in August, 1950, because of two months of epigastric gnawing and cramping pain with progressive jaundice. The physical findings were unremarkable. A blood count was normal. Urinalysis showed a trace of albumin and numerous pus cells. A fasting preoperative blood sugar value was 108 mg. per 100 ml. Serum bilirubin was 25.0 mg. per 100 ml. (direct); cephalin-cholesterol flocculation, 4 plus in 24 hours; thymol turbidity,

1.0 unit; prothrombin time, 14 sec.; and serum amylase, 180 units.

A total pancreatectomy was performed for an adenocarcinoma of the pancreas. There was no visible hepatic disease. During the first four postoperative days, the insulin requirement ranged from 40 to 50 units of regular insulin given at intervals of from two to four hours depending on the degree of glycosuria. When the diet reached 180 gm. of carbohydrate and 1,800 calories daily, 10 to 20 units of PZI was added each morning.

On the twenty-sixth postoperative day the patient was discharged and advised to take the following regimen: diet, 2,400 calories (CHO:220;P:128;F:12); a mixture of 10 units of PZI and 40 units of regular insulin daily; pancreatic extract, 15 grains three times daily; Ketochol* tablets, one three times daily; and choline dihydrogen citrate liquid, 1 dram three times daily. The patient's progress was satisfactory; there were one or two normal stools daily until about three months later when the patient was readmitted to the hospital because of abdominal pain secondary to extensive metastatic disease. A bilateral splanchnicectomy was performed; there resulted no significant change in the severity of the diabetes. Until the time of the patient's death, fifteen days after admission, the insulin requirement remained at about 10 units of PZI plus 10 units of regular insulin daily, given separately each morning while the patient was following a 2,300-calorie diet containing 220 gm. of carbohydrate. The patient had survived four months after total pancreatectomy. Necropsy was not permitted.

Case 9. A thirty-three-year-old white woman was first seen in January, 1954, because of a previous diagnosis of "a common duct stone." The physical findings showed no abnormality except a mild degree of scleral icterus. Total serum protein was 6.9 gm. per 100 ml.; serum albumin, 3.8 gm. per 100 ml.; serum globulin, 3.1 gm. per 100 ml.; serum amylase, 930 units; serum bilirubin, 39 mg. per 100 ml. (direct), 98 mg. per 100 ml. (indirect); cephalin-cholesterol flocculation, negative in twenty-four hours; thymol turbidity, 1.3 units; and prothrombin time, 100 per cent. A blood count, urinalysis, blood urea, blood Wassermann and Kahn tests were normal. A preoperative fasting blood sugar value was 100 mg. per 100 ml.

A total pancreatectomy was performed for carcinoid of the ampulla of Vater with extension to the pancreas. The liver was apparently normal. During the first five postoperative days, 6 to 10 units of insulin was given every four hours to control glycosuria; blood sugar values ranged from 100 to 400 mg. per 100 ml. To each liter of 5 per cent dextrose was added 10 units of regular insulin during this period. By the twelfth postoperative day blood sugar values had reached normal. The patient was taking 16 units of NPH insulin before breakfast and from 1,993 to 2,123 calories daily with an average carbohydrate intake of 200 gm.

On the twenty-first postoperative day she was discharged and advised to take 10 units of NPH insulin, to follow a 2,533-calorie diet (CHO:240;P:112;F:125), and to take Bilron capsule one twice daily, pancreatic extract 15 grains three times daily, and vitamins. About three months later she developed pain in the right upper quadrant of the abdomen. An exploratory laparotomy revealed an inflammatory reaction involving the liver and several loops of small bowel, which necessitated drainage and irrigation of a pelvic abscess extending into the abdominal wall. Since then the patient has done well while taking 10 to 20 units of NPH insulin each morning, and a 1,935-calorie diet (CHO:220; P:86;F:79), extra vitamins, and pancreatic extract tablets (60 grains) daily. The patient has survived more than three years after total pancreatectomy.

Case 10. A sixty-five-year-old white man was first seen in 1954 because of painless jaundice, anorexia, and occasional diarrhea, of about one week's duration. Physical findings showed only moderate scleral icterus. A blood count was normal; casual urinalysis yielded "4 plus" sugar; fasting preoperative blood sugar, 500 mg. per 100 ml.; prothrombin time, 86 per cent; total serum protein, 7.0 gm. per 100 ml.; serum albumin, 4.0 gm. per 100 ml.; serum globulin, 3.0 gm. per 100 ml.; serum bilirubin, 1.1 mg. per 100 ml. (direct) and 5.0 mg. per 100 ml. (indirect); cephalin-cholesterol flocculation, negative in twenty-four hours; thymol turbidity, 2.1 units; alkaline phosphatase, 12.9 Bodansky units; serum phosphorus, 5.2 mg. per 100 ml.; serum amylase, 61 units. Diabetes mellitus was fairly well controlled preoperatively: the blood sugar values ranged from 130 to 200 mg. per 100 ml. The patient was taking 60 units of NPH insulin each morning and was following a 2,120-calorie diet (CHO:250;P:100;F:80).

A total pancreatectomy was performed for adenocarcinoma of the pancreas; the liver appeared normal. During the first four postoperative days the blood sugar values ranged from 200 to 300 mg. per 100 ml. fasting, with normal blood sugar values at 4 p.m. while on 30 units of NPH insulin at 7 a.m. and 5 units of regular insulin at 11 a.m. To each liter of 5 per cent dextrose was added 10 units of regular insulin during this time. The insulin requirement was about the same during the remaining postoperative period. On the twenty-fourth postoperative day the patient was discharged; he was taking 20 units of NPH insulin daily and was following a diet containing 2,470 calories (CHO:250;P:120;F:110).

Maintenance of body weight and control of diarrhea were fairly well achieved with pancreatic extract, 15 grains three times daily, and Sorlate,* two capsules three times daily. The insulin requirement remained between 15 and 25 units of NPH insulin each morning. During the next twelve months he was readmitted to the hospital three times because of cramping abdominal pain. On the last admission, an exploratory laparotomy revealed partial obstruction of the small bowel because of recurrent carcinoma. The patient died at home and the details of his death were not obtainable. The patient had survived fourteen months after total pancreatectomy.

DISCUSSION

As one would expect, the insulin requirements of pancreatectomized patients in the immediately postoperative period are different from those in the later period. In the first period the insulin requirements vary tremendously; in the second period they become more stabilized when the patient maintains a more evenly regulated daily intake of food and perhaps also a more even ab-

*Ketochol—250 mg. tablet (G. D. Searle & Co., Chicago)—products of unconjugated bile acids obtained from bile.

*Sorlate capsules—7½ grains (Abbott Laboratories, North Chicago)—each capsule containing 7½ grains of Polysorbate 80, Abbott.

sorption of food. Uniform control for the early postoperative period is difficult for many reasons, among which are: (1) relative sensitivity to insulin in most patients; (2) irregular intake of food; and (3) decreased absorption of food often associated with (4) diarrhea, (5) postoperative stress, and (6) absorption of toxic products from the operative site. Severe reactions to insulin are prone to occur, and may even be fatal. Doses as high as 100 units of insulin daily have been administered without producing insulin reactions, and there have been patients who required no more than 10 units daily and whose blood sugar values fluctuated between normal and as high as 400 mg. per 100 ml. throughout the day. It is interesting to speculate whether accessory islet tissue is present and functioning in some of the patients whose insulin requirements were as low as 10 units per day.

Most of these patients ultimately required only 10 to 30 units of insulin daily (table 4), but this range of requirements does not reflect mildness of the diabetes in terms of ease of control. It is widely recognized that the severity of diabetes cannot be graded simply by the amount of insulin required. In many patients having spontaneous diabetes who require as much as 60 units of insulin daily, the diabetes may be easily controlled; whereas "brittle" diabetes in patients who may tolerate no more than 20 to 30 units of insulin per day may defy the clinician's ability to establish satisfactory control. It has been observed that after total pancreatectomy in a known diabetic, the daily insulin requirement is not increased and may, in fact, be decreased.[8] It already has been established that after total pancreatectomy, patients may require less insulin than do many spontaneous diabetics.[9] In this series three patients (Cases 1, 4, and 10) had diabetes that was discovered only a few days before total pancreatectomy and comparison of the preoperative and postoperative diabetic courses was not possible. The extent of pancreatic tissue involvement by tumor, fibrosis, and inflammation could not be correlated with the findings of diabetes before pancreatectomy.

Dogs which have undergone total pancreatectomy are sensitive to insulin, and frequently insulin shock causes death.[11] In man, similar effects have been reported, although marked variations in this respect are apparent, as will be shown later. Because many patients who have undergone pancreatectomy are insulin-sensitive and because the hypoglycemic attacks may be very severe and dangerous, it was found advisable to permit some hyperglycemia and glycosuria, attempting always to avoid ketosis, polyuria, and, if possible, loss in weight.

In two patients (Cases 2 and 5) symptoms simulating

TABLE 4

Summary of the diabetic course in ten patients

Case No.	Present Status of Control of Diabetes in Living Patients	Average Insulin Dosage in Units: Early Postop.	Average Insulin Dosage in Units: On Discharge	Blood Sugar Range (mg./100 ml.)	Caloric Intake on Discharge	Postop. Weight Loss lb.	Diarrhea	Effect of Pancreatic Extracts on Diarrhea
1	—	Preop. 40 NPH Postop. 30 NPH	10-30 NPH	75-428	1,712 (CHO:200;P:120;F:48)	15	Present	Partially controlled
2	—	25 NPH	35 NPH	59-333	2,038 (CHO:181;P:99;F:102)	Not recorded	Absent	Refused by patient
3	—	30 NPH	10 NPH	50-212	1,884 (CHO:205;P:86;F:80)	20	Absent	*
4	—	25 PZI 60 Reg.	15 PZI 15 Reg.	21-423	1,827 (CHO:160;P:74;F:99)	15	Absent	None prescribed
5	—	50 PZI 15 Reg.	10-15 PZI 10-20 Reg.	47-511	2,600 (CHO:250;P:120;F:140)	25	Absent	*
6	—	20 PZI	20 PZI	58-363	1,400 (CHO:145;P:71;F:60)	26	Absent	None prescribed
7	—	12 NPH 15 Reg.	18 NPH	104-575	1,637 (CHO:180;P:83;F:65)	43	Absent	None prescribed
8	—	15 PZI 35 Reg.	10 PZI 40 Reg.	78-410	2,400 (CHO:220;P:128;F:12)	13	Absent	*
9	Good	12 NPH	10 NPH	100-350	2,533 (CHO:240;P:112;F:125)	20	Absent	*
10	—	Preop. 60 NPH Postop. 30 NPH 5 Reg.	20 NPH	100-500	2,420 (CHO:300;P:125;F:80)	30	Mild	Controlled

*Prescribed prophylactically.

insulin reactions occurred during the postoperative period. They manifested left hemiparesis, lethargy and mental confusion. However, these symptoms proved not to be insulin reactions, on the basis of blood sugar values that were normal or high, and because of failure to respond to intravenous administration of dextrose.

Some severe insulin reactions did occur (Cases 4 and 5). In Case 4, the patient had required large amounts of insulin, approximating 100 units per day, to maintain control of the blood sugar values. In other cases of this type, the withdrawal of insulin has resulted in the development of severe diabetic acidosis within twenty-four to forty-eight hours. In this patient it appeared that relatively sudden insulin sensitivity developed. This was one of the first pancreatectomies performed here and, in retrospect, it is unfortunate that PZI was used. It may have been that it had a cumulative effect. On the day that the reaction occurred (table 3, day 6), glucose was given intravenously, and symptoms promptly disappeared. Subsequently, there were no symptoms of hypoglycemia although the blood sugar values remained low until the eleventh postoperative day. No insulin was given from the ninth to the twelfth postoperative days with blood sugar values ranging between 21 and 85 mg. per 100 ml. It is interesting that extremely low blood sugar values persisted so long without any noticeable symptoms. The patient maintained a normal daily caloric intake and had no diarrhea.

Insulin requirements of each patient during the late postoperative phases are shown in table 4. Individual daily caloric intake at that time ranged from 1,400 to 2,600 calories with the carbohydrate content of the diet ranging from 145 to 250 gm.

According to our criteria for the control of diabetes, the disease was not successfully controlled in any of these patients. The factors that cause resistance to control may relate inherently to the type of diabetes occurring after the operation, or they may be secondary to the many factors that affect the general metabolic status. During the administration of insulin, acidosis was not a problem in any of the patients, although at times the blood sugar values were high for periods of weeks. The marked instability of the diabetes as judged by extremely rapid variation in blood sugar values in these patients is reminiscent of the situation so frequently encountered in unstable (juvenile) spontaneous diabetes. In some of the latter patients the pancreatic insulin and blood insulin concentrations are extremely low.[5]

It has been demonstrated that when pancreatic extract is not administered, caloric absorption after pancreatectomy may be approximately 25 to 30 per cent below the caloric intake.[12] Carbohydrates are well absorbed despite the absence of the pancreas, although proteins and fats are not. Protein excretion in terms of fecal nitrogen is two to seven times that of the normal person. Fat excretion in a normal person on an intake of 100 gm. of fat per day is approximately 6 to 7 gm.; whereas, after pancreatectomy, patients on equivalent intake have been reported to excrete as much as from 36 to 48 gm. daily.[13] Therefore, the caloric intake of the patient after pancreatectomy should, if possible, be increased by at least 40 per cent to compensate for decreased absorption.[13] This may be a difficult task in the patient with metastatic carcinoma whose condition is rapidly deteriorating.

Pancreatic extract is claimed to aid fat absorption and to have little effect upon protein absorption, which may account for the frequent difficulty in inducing a satisfactory gain in weight of some pancreatectomized patients. However, one patient in this series refused to take the extract while for three others it was not prescribed, generally without ill effect. There was no apparent difference in the insulin requirements of those who did and those who did not take pancreatic extract.

Three patients (Cases 1, 4, and 10) were diabetic prior to total pancreatectomy. After operation no real change in diabetic status was apparent, and no definite change in sensitivity to insulin was demonstrated.

SUMMARY AND CONCLUSIONS

Complete control of diabetes following total pancreatectomy is difficult to achieve, and insulin reactions are prone to be severe and may even be fatal; it appears prudent to aim at partial control of the diabetes and to permit variable degrees of hyperglycemia and glycosuria. There are great differences in individual insulin requirements after total pancreatectomy. Among the patients in this series who were able to maintain a caloric intake of from 1,400 to 2,600 calories daily with the carbohydrate content ranging from 145 to 250 gm., the daily insulin doses varied from 10 to 50 units per day (average, approximately 25 units per day).

In spite of vigilance, four of our patients experienced severe insulin reactions, although three of them were being given very small amounts of insulin. It seems certain that an insulin reaction caused the death of one patient (Case 4). Insulin coma with secondary cerebral damage was considered to be a possible cause of death of two patients (Cases 2 and 5), but failure to obtain permission for a necropsy prevented verification of this possibility (table 1).

The ten patients were maintained on a relatively high-carbohydrate, high-protein, low-fat diet, but because inability to gain weight was a constant problem, the diets

eventually were liberalized to coincide with the patient's wishes. Despite the absence of pancreatic-enzyme replacements, some patients continued to have normal bowel movements, ranging from one to three per day.

The survival time of these patients is too short to permit adequate observations regarding the incidence of chronic complications of diabetes following pancreatectomy. In eight patients eye examinations disclosed no retinopathy. The longest survival time was thirty months. One survived four years but had no eye examination. One is alive and well four years postoperatively and has no retinopathy or other diabetic complications.

There were no operative deaths. However, because of the very high incidence of morbidity and the early deaths due to the underlying disease, which was not cured by this procedure, it is unlikely that total pancreatectomy will again be performed for carcinoma by surgeons of this institution.

SUMMARIO IN INTERLINGUA

Observationes Clinic Relative A Diabete Post Pancreatectomia Total: Reporto De Dece Casos

Completitate del control de diabete post pancreatectomia total es difficile a effectuar. Sever reactiones a insulina debe esser expectate. Illos mesmo pote resultar in le morte del patiente. Per consequente il pare prudente visar al control partial del diabete e admitter variabile grados de hyperglycemia e de glycosuria. Le requirimentos de insulina post pancreatectomia total varia grandemente ab un individuo al altere. Inter le patientes del presente serie qui esseva capace a mantener un ingestion diurne de inter 1.400 e 2.600 calorias, con un contento de hydratos de carbon de inter 145 e 250 g, le doses diurne de insulina variava inter 10 e 50 unitates (con un dosage medie de circa 25 unitates per die).

In despecto de nostre vigilantia, quatro del patientes experientiava sever reactiones a insulina, ben que tres de illes recipeva solmente micrissime quantitates. Il pare certe que un reaction a insulina esseva responsabile pro le morte de un patiente (Caso 4). Coma de insulina con secundari lesiones cerebral esseva considerate como possibilemente le causa del morte de duo altere patientes (Caso 2 e Caso 5), sed proque le necropsia esseva refusate in iste casos, nulle verification esseva possibile.

Le dece patientes esseva mantenite a un dieta relativemente ric in hydrato de carbon e in proteina e povre in grassia, sed proque le non-augmento de peso remaneva un constante problema, le dietas esseva liberalisate in le curso del tempore de accordo con le desiros del patientes individual. In despecto del absentia de reimplaciamento del enzymas pancreatic, alicunes del patientes continuava evacuar lor intestinos normalmente.

Le periodo de superviventia postoperatori de iste patientes non es satis longe pro permitter adequate observationes relative al incidentia de complicationes chronic de diabete post pancreatectomia. In octo patientes, examines ocular revelava nulle retinopathia. Le plus longe periodo de superviventia postoperatori esseva trenta menses. Un patiente superviveva quatro annos, sed su oculos non esseva examinate. Un altere patiente in le serie vive e se trova ben quatro annos post le operation. In su caso, ni retinopathia ni altere complicationes de diabete ha occurrite.

Nulle del patientes moriva al operation. Tamen, a causa del alte incidentia de morbiditate sequite tosto in consequentia del subjacente morbo (que non esseva curate per le intervention chirurgic), il es pauco probabile que pancreatectomia va de novo esser usate per chirurgos de iste establimento in le effortio de tractar carcinoma.

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Diabetes Mellitus in Association with Primary Carcinoma of the Pancreas

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The association of diabetes mellitus and primary carcinoma of the pancreas has been noted for at least a century. Early French clinicians[1,2] reported several such cases, but there have been relatively few critical comments on the relationship, or lack of relationship, between the two diseases. A further study of the problem was therefore undertaken.

MATERIAL AND METHOD

The study was based on the necropsies in 209 consecutive cases of primary carcinoma of the pancreas at the Mayo Clinic from 1926 to 1952. Information was obtained from the clinical records, gross specimens and histologic sections. The location of the neoplasm was designated as either the head or the body of the organ. The phrase "body of the pancreas" refers in this study to the body or tail of the gland, or both. The neoplasms were classified histologically as either ductal, acinar or indeterminate in origin. The size of the tumor was expressed as the mean of the three greatest dimensions.

The diagnosis of diabetes mellitus was based on one or more fasting venous blood-sugar values of 120 mg. per 100 cc. or more by the Folin-Wu method, with or without glycosuria. Glucose-tolerance tests were not generally employed. It should be noted that in a group of ill patients such tests frequently yield false positive results owing to factors not related to diabetes.

An analysis was made of the relation between the size, cell type and location of the pancreatic tumor, on the one hand, and the presence or absence of diabetes on the other. An effort was made to evaluate the factor of hereditary predisposition to diabetes by study of the family histories.

RESULTS

The frequency of glycosuria and frank diabetes in the 209 cases is shown in table 1. Diabetes was present in forty-one cases (19.6 per cent). Of these, diabetes was known to have been present in nine (4.3 per cent) prior to the development of symptoms of carcinoma; in the remaining thirty-two (15.3 per cent), diabetes was discovered after the onset of symptoms referable to the neoplasm. An additional group, sixty-one patients (29.2 per cent), was found to have glycosuria one or more times but a diagnosis of diabetes was not or could not be established. There remained 107 patients (51.2 per cent) in whom no evidence of diabetes or glycosuria was found. In all groups the age and sex distribution, average size of the tumor and distribution of grades of malignancy were similar.

TABLE 1

Primary carcinoma of the pancreas in relation to diabetes: classification of 209 patients

Group	Patients	Per cent
Diabetes present before onset of symptoms of pancreatic carcinoma	9	4.3
Diabetes found after onset of symptoms of pancreatic carcinoma	32	15.3
Diabetes not diagnosed, but glycosuria present	61	29.2
No diabetes or glycosuria	107	51.2
Total	209	100.0

Cases in which diabetes mellitus was known to be present prior to onset of symptoms of pancreatic carcinoma. The average age at which diabetes was discovered in the nine cases in this group was 52.7 years. The average interval between the diagnosis of diabetes and the onset of symptoms of pancreatic carcinoma was 9.7 years (range, 1.5 to 22 years). There was a preponderance of the more severe grades of diabetes in this group, insulin being required in eight of the nine cases. Of eight cases in which information was available, there was a family history of diabetes in four. The neoplasms of the nine patients in this group were located in the head of the pancreas in five and in the body in four. Six of the nine tumors were of the ductal cell type and three were of the acinar type.

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Cases in which diabetes mellitus was discovered after onset of symptoms of pancreatic carcinoma. Of the thirty-two patients in this group, only seven had cardinal symptoms of diabetes. Fasting blood-sugar values ranged from 120 to 400 mg. per 100 cc., the average being 182 mg. The diabetes in this group was predominantly mild, insulin being required in only five of the thirty-two cases. Among thirty patients for whom information was available, only four patients had a family history of diabetes. The carcinomas were located in the head of the pancreas in twenty-six cases and in the body in the remaining six. In thirty cases the tumors originated from ductal cells and in two from acinar cells. There was no correlation between size of tumor and severity of diabetes.

An attempt was made in this group to evaluate by simple inspection of microscopic sections the effect of the neoplasm on the remaining uninvolved pancreas, particularly the islet tissue. Extensive fibrosis and some apparent reduction of the amount of islet tissue were found in association with some tumors of either the head or the body of the pancreas but particularly the head. However, extensive fibrosis and reduction of the amount of islet tissue were present in only about a third of the cases of diabetes, while in the remaining two-thirds there was at most only minimal evidence of fibrosis along with an apparently normal number of islets. It appeared doubtful that actual destruction of islet tissue was sufficiently pronounced in most of the thirty-two cases to account for the presence of diabetes.

Cases in which a diagnosis of diabetes was not established. This group totaled 168 cases, including sixty-one* in which glycosuria occurred and 107 in which it did not.

Among 127 cases in the group without diabetes in which information was available, only ten patients had a family history of diabetes. Among the entire group of 168 cases the carcinomas were located in the head of the pancreas in 121 and in the body in forty-seven. There were 141 carcinomas arising from ductal cells and seventeen from acinar cells, while ten were of indeterminate origin. Among the 168 cases in which diabetes was not demonstrated, the fasting blood sugar was determined in thirty-three and was normal in all instances.

Correlations between incidence of diabetes following pancreatic carcinoma, and location and type of tumor and family history of diabetes. The difference in incidence of diabetes in association with tumors of the head (17.7 per cent) and body (11.3 per cent) is not significant, for this difference would occur by chance 28 per cent of the time. Likewise, the difference in incidence of diabetes in association with ductal cell lesions (17.5 per cent) and acinar cell lesions (10.5 per cent) is not statistically significant, for this difference would occur by chance 43 per cent of the time. Even the difference in incidence of diabetes in association with positive (28.6 per cent) and negative (17.0 per cent) family history of diabetes is not significant, for the observed difference here would occur by chance 25 per cent of the time.

Thus, in this series of cases in which diabetes was discovered after the onset of symptoms of primary carcinoma of the pancreas, neither size, cell type, grade of malignancy or location of the tumor nor family history appeared to be a determining factor in the development of diabetes. It is, of course, possible that a larger series of cases might bring out significant differences in the incidence of diabetes in relation to these factors.

COMMENT

Several questions arise from this study. Does the prior presence of diabetes predispose to the development of carcinoma of the pancreas? In this series of 209 cases of primary carcinoma of the pancreas there were nine (4.3 per cent) in which diabetes was present before the onset of symptoms of pancreatic neoplasm. Warren and LeCompte,[3] Marble,[4] and McKittrick and Root[5] have reported a total of twenty-five similar cases. Neither their data nor ours permit an answer to the question of whether the prior presence of diabetes predisposes to the development of carcinoma of the pancreas.

Does the presence of carcinoma of the pancreas give rise to diabetes in an appreciable number of cases? In this series it appears that coexistence of the two diseases was too frequent to be explained as coincidence, for in 15.3 per cent the presence of diabetes was established after the onset of symptoms of carcinoma of the pancreas. However, as Berkson[6] has emphasized, the coexistence of two diseases does not necessarily imply a cause-and-effect relationship but may be related to a variety of factors, particularly peculiarities of selection of cases.

What relationship exists between location of tumor and development of diabetes? It has been suggested by Grauer[7] that tumors in the head of the pancreas are particularly prone to cause diabetes owing to obstruction of

* Among the sixty-one cases in which glycosuria was found one or more times after the onset of symptoms of carcinoma but in which a diagnosis of diabetes mellitus was not established, twenty patients had normal values for fasting blood sugar, while in the remaining forty-one no determinations of blood sugar were recorded. In thirty of the sixty-one cases glycosuria coincided with the parenteral administration of glucose and hence was of doubtful significance.

the pancreatic ducts with subsequent fibrosis and damage to the islet tissue. In a study of the effects of duct ligation in rabbits, cats and dogs, Ssobolew[8] found that 30 to 120 days after ligation, sclerosis of the islets took place, and glycosuria sometimes occurred. Silver and Lubliner,[9] in an effort to explain the occurrence of diabetes in association with tumors in the body and tail of the pancreas, suggested that diabetes in such cases may be due to destruction of a portion of the pancreas containing the greatest concentration of islet tissue. However, none of the foregoing observations and speculations seem adequate to explain most of the instances of diabetes in the present study. Tumors in the head of the pancreas did not appear to have a significantly more frequent association with diabetes than did tumors of the body. Furthermore, among the thirty-two patients who were found to have diabetes after the onset of symptoms of carcinoma, extensive pancreatic fibrosis and destruction of islets were present in only about a third. It would thus appear that actual destruction of islet tissue owing to the presence of the neoplasm is not the sole basis for the development of diabetes. The possible presence in some cases of mild unrecognized diabetes prior to the development of carcinoma cannot be ruled out, nor can the factor of hereditary predisposition to diabetes be accurately evaluated solely on the basis of family history. Nevertheless, it would appear that the incidence of diabetes after the onset of symptoms of carcinoma in this study is higher than would be anticipated in the general population of comparable age.

In spite of the fact that only one patient in six in this study was proved to have diabetes following pancreatic carcinoma, it would appear to be good clinical judgment to consider the possibility of such a lesion in any patient with persistent vague abdominal pain and newly discovered diabetes.

SUMMARY

Two hundred and nine cases of primary carcinoma of the pancreas were reviewed after necropsy in an effort to determine the incidence of diabetes and the relationship between diabetes and the pancreatic tumor.

Nine patients (4.3 per cent) had diabetes prior to the onset of symptoms of pancreatic carcinoma. No conclusions could be reached regarding the question of whether the prior presence of diabetes predisposes to the development of carcinoma of the pancreas.

Another thirty-two patients (15.3 per cent) were found to have diabetes after the onset of symptoms of pancreatic carcinoma. The presence of diabetes was not, or could not be, established in 168 (80.4 per cent) of the patients. Among the patients in whom the presence of diabetes was established after the onset of symptoms of carcinoma of the pancreas, there seemed to be no significant relationship to type, location and size of the neoplasm. In at least two-thirds of the cases in which diabetes appeared after the development of symptoms of neoplasm, there did not appear to be sufficient destruction of islet tissue by fibrosis, tumor invasion or inflammation to account for the presence of diabetes.

It seems probable that the two factors of hereditary predisposition to diabetes and actual destruction of islet tissue owing to the presence of neoplasm, although not shown to be individually significant in the entire series, might in combination account for the observed instances of diabetes. However, other unrecognized factors, including peculiarities of selection of cases in this series, cannot be excluded.

SUMMARIO IN INTERLINGUA

Diabete Mellite In Association Con Primari Carcinoma Del Pancreas

Duo centos e nove casos de primari carcinoma del pancreas esseva studiate al necropsia con le objectivo de determinar le incidentia de diabete e le relation inter diabete e le tumor pancreatic.

Nove patientes (4,3 pro cento) habeva diabete ante le declaration de symptomas de carcinoma pancreatic. Nulle conclusiones esseva derivate con respecto al question de si le presentia anterior de diabete predispone al disveloppamento de carcinoma del pancreas.

Esseva trovate que trenta-duo patientes additional (15,3 pro cento) disveloppava diabete post le declaration del symptomas de carcinoma pancreatic. Le presentia de diabete non esseva establite o non poteva esser establite in 168 del patientes (80,4 pro cento). In le gruppo de patientes in qui le presentia de diabete esseva establite post le declaration del symptomas de carcinoma del pancreas, il non pareva exister ulle correlation significative con le typo, le loco, e le dimension del neoplasma. In al minus duo tertios del casos in que diabete appareva post le disveloppamento de symptomas de neoplasma, le grado de destruction del histos insular per fibrosis e le grado de invasion tumoric o de inflammation non sufficeva pro explicar le presentia de diabete.

Il pare probabile que le duo factores de predisposition hereditari al disveloppamento de diabete e de ver destruction de histos insular in consequentia del presentia de neoplasma (ben que illos non se monstrava individualmente significative in le serie integre) es capace, in combination, a explicar le observate casos de diabete. Tamen, altere, non-recognoscite factores—incluse peculiaritates del selection de casos in le presente serie—non pote esser excludite.

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DISCUSSION

PHILIP M. LECOMPTE, M.D., (*Boston*): I should like to ask if the authors used any quantitative methods for determining the amount of beta cell granulation in the pancreas. The reason I ask this is because, in order to determine the actual mass of functioning beta cell tissue in the pancreas, it is necessary to use quantitative methods, such as those of Ogilvie. The reason I bring up this point is that it is conceivable that in some cases the amount of beta cell tissue may be reduced already to a considerable extent, and then the superimposition of a carcinoma might be enough to diminish the mass of beta cells to such a point that diabetes would appear.

ALEXANDER MARBLE, M.D., (*Boston*): Over the years there has been a great deal of discussion as to whether or not cancer is more common among diabetic than nondiabetic individuals. Certain workers have published data which suggest that cancer occurs more commonly in diabetics than in the general population. However, on each occasion that we have analyzed our own data, we have been forced to conclude that there is no conclusive evidence that this is true.

In the study by Dr. Green and his associates, the matter has been approached from the other direction. They have attempted to answer the question whether diabetes is found more commonly among persons with cancer and specifically among those with primary carcinoma of the pancreas. I have no personal data of exactly this type to report but it may be of interest that among our diabetic patients, those with cancer of the pancreas have comprised a significantly higher percentage of the total number of diabetic patients with cancer than is true in the general population. Thus, in our patients, cases of cancer of the pancreas have formed 8 to 13 per cent of the total of those with cancer whereas in the general population cancer of the pancreas constitutes about 4.5 per cent of all types of malignant disease.

Studies carried out during the past few years at the Memorial Center for Cancer and Allied Diseases in New York City by Glicksman, Myers and Rawson (*Med. Clin. N. Amer.* 40:887, 1956; *Cancer* 9:1,127, 1956) demonstrated abnormal glucose tolerance curves in 36.7 per cent of 628 patients with a tissue diagnosis of cancer as contrasted with only 9.3 per cent positive results in a control group of 322 patients with tumors proved to be benign. Known diabetics were not specifically excluded from the study; they consisted of 4.4 per cent of the control group and 13 per cent of the cancer group. In this study there were only five patients with cancer of the pancreas but four of these showed abnormal glucose tolerance tests.

The relatively high incidence of abnormal glucose tolerance tests among individuals with cancer has been a subject for comment and speculation for many years. In a discussion of the total problem, a distinction should be made between the incidence of abnormal tolerance curves and frank diabetes from a clinical standpoint.

I would like to ask Dr. Green two questions: (1) Have you studied patients with other types of carcinoma as regards possible diabetes in the same manner that you have done with those with carcinoma of the pancreas? If so, what were the results? (2) I believe that you stated that patients were considered to have diabetes if the fasting blood sugar was 120 mg. per 100 cc. or higher, with or without glycosuria. Were there many of the positive cases whose values were borderline with only one or two values of, say, 120 mg. per cent?

DR. GREEN: No quantitative method was used to determine the amount of beta cell granulation in the pancreas of these cases, and no attempt was made to evaluate accurately either the number or the functioning capacity of the islets. Our statement that one third of the diabetic cases had an apparent decrease in the number of islets was only an impression since no special staining technics were used and only routine sections of the pancreas were examined.

In answer to Dr. Marble's first question, I do not believe there have been at the Mayo Clinic any similar studies with other types of malignancy. Certainly, additional studies should be carried out.

In response to Dr. Marble's second question, there were only three patients with borderline blood sugar levels. The remaining cases had a marked elevation of their blood sugar levels.

A Comparison of Benedict's and the Glucose Oxidase Tests for the Mass Detection of Diabetes

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Since hospitals in the United States report approximately sixty-five million outpatient visits each year, the Commission on Chronic Illness[1] has recommended that screening procedures to detect unsuspected chronic illness be applied to this readily accessible group of patients. The initiation of early treatment for such diseases represents "secondary prevention" (prevention of progression), which offers the best hope of interrupting the natural course of diseases for which primary preventive measures (to prevent onset) are not available. Before applying detection tests to such a population group, it is necessary to scrutinize carefully the validity of the tests employed, in terms of sensitivity and specificity,[2] so that excessive retesting procedures upon those who do not have the disease will be reduced to a minimum. Simple urine sugar tests employing papers impregnated with an enzyme (glucose oxidase), which measures true glucose only, have recently become available. Evaluation of their usefulness in mass diabetes detection programs is desirable. The present study compares these newer enzyme tests with older copper reduction tests (Benedict's copper reagent as solution or tablet),* which measure total reducing substances.

MATERIALS AND METHODS

Tests were performed upon approximately 8,000 persons applying to the John Gaston Hospital Out-Patient Department Clinics for periodic detection tests or for admission to clinics. Periodic detection tests are provided not only for diabetes but also for syphilis, tuberculosis, cervical cancer and glaucoma. Only persons over thirty years of age were tested for diabetes, and pregnant women were excluded from this study.

The urine tests employed consisted of Benedict's qualitative test (solution and tablet), which measures total reducing substances, and glucose oxidase papers A and B,† which are enzyme tests that measure true glucose only. Comparative data will be presented first on 4,000 persons who were tested using these four urine sugar tests (Group I). A separate analysis was later made upon a group of similar size when it became apparent that improved products for enzyme testing of urine glucose had subsequently become available, overcoming some of the shortcomings noted during the study of the first group. In fairness to these products, it was decided to carry out an additional study employing the improved products, and comparing their performance with the test using that of Benedict's solution (Group II).

A specimen of urine was obtained from each person tested. If any of the four urine tests was positive (except for trace reports with Benedict's solution, which were ignored) a preliminary blood sugar determination by the Folin-Wu method was done. The elapsed time since the last meal was recorded, and when the blood sugar was below 130 mg. on a fasting specimen (4 hr. after last meal), or below 180 mg., 140 mg., or 130 mg. respectively, one, two, or three hours postprandial, a modified glucose tolerance test was performed as follows: 100 gm. of glucose was given p.o. and fasting and two-hour blood sugar determinations (Folin-Wu) were done. Persons showing values above 140 mg. on the two-hour specimen were referred to the Medicine Clinic for further evaluation. Those showing blood sugar values which exceeded the above levels on the preliminary blood sugar test were tentatively considered to be diabetic and were referred directly to the Medicine Clinic for definitive diagnosis. Since almost all of the persons tested were eligible for outpatient clinic services and evaluation, comparatively uniform standards of diagnosis were assured.

The desirable interval after eating for performing urine or blood sugar tests has been designated as either one or two hours.[2] It became obvious to us, however, that it was impossible to achieve such ideal conditions in a group of the type under study. Only 30 per cent of

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*The copper reagent tablet used was Clinitest made by Ames Company, Inc.

†Oxidase paper A = Tes-Tape, supplied by Eli Lilly and Company, and oxidase paper B = Clinistix, supplied by Ames Company, Inc.

our group were tested either one or two hours after eating, while 49 per cent were fasting at the time of the test. Tests while fasting are notoriously unreliable, but this circumstance was beyond our control.

PRESENTATION OF DATA

Table 1 shows the results of our diabetes detection program, employing urine tests, for the two groups of our study. An identical percentage (1.0 per cent) of previously unknown diabetics was found in both groups. A somewhat higher percentage (2.2 per cent) of previously known diabetics was encountered in the second group than in the first group (0.9 per cent).

TABLE 1

Results of diabetes detection by urine tests in two groups

	Group I		Group II	
	Number	Per Cent	Number	Per Cent
Persons tested	4,000	100.0	3,991	100.0
Positive urine tests	134	3.4	198	5.0
Previously unknown diabetics	39	1.0	39	1.0
Previously known diabetics	36	0.9	89	2.2
False positive tests				
Technical	25	0.6	21	0.5
Renal glycosuria	13	0.3	18	0.4
Incomplete	24	0.6	31	0.8

Two categories of false positive tests are designated: "technical" and "renal glycosuria." Technical false positive tests represent those positive on the preliminary urine screening test but subsequently negative during the modified glucose tolerance test described above. These are false positive in the sense that diabetes was not ultimately diagnosed, rather than in denoting technical error or absence of sugar in the urine. The category of renal glycosuria includes those positive on the preliminary screening test and also showing a positive urine test during the glucose tolerance test in the presence of a comparatively low blood sugar level, suggesting a low renal threshold. Strictly speaking, the latter are not falsely positive, since reducing substances are actually present in the urine and it is of some value to identify these individuals so that they are not mistakenly labeled as diabetics. For this reason, only the former group of "technical" false positives will be examined when comparison is made of the relative specificity of the urine tests under consideration.

In the analysis to follow, information relating to the ability of the tests studied to give a "yes" or "no" answer was of sole concern. This is a different consideration than would apply to the use of these tests in the management of diabetics under therapy, where quantitative results might be desired. Our evaluation was based solely on the accuracy of the tests in discovering new diabetics in the groups studied (sensitivity) and in designating as normal those without the disease (specificity). Since it was impractical to perform definitive procedures to rule out or rule in diabetes in each individual included in our study, the latter should be viewed as a comparison of the relative sensitivity and specificity of the tests under consideration.

GROUP I

This group of 4,000 persons consisted wholly of applicants for periodic detection tests. Seventy per cent of these were colored females, 12 per cent were white females, and the remainder were colored and white males in the same proportion. The females represented for the most part domestic servants applying for employment health cards.

Table 1 shows the results obtained by screening this group with four urine sugar tests: Benedict's solution, Benedict's tablet, oxidase paper A, and oxidase paper B. One hundred thirty-four persons (3.4 per cent) out of 4,000 tested were positive to one or more of the urine sugar tests employed. In this group thirty-nine previously unknown diabetics (1.0 per cent) were discovered.

If the performance of the tests in relation to these thirty-nine previously unknown diabetics is considered as a measure of the relative sensitivity of the tests employed, it will be noted from table 2 that Benedict's tablet proved less sensitive than Benedict's solution, missing ten diabetics who were screened as positive by the latter test. Oxidase paper A missed an almost equal number (eleven) and oxidase paper B missed a smaller number (seven) of those who screened positive with Benedict's solution. Of interest is the observation that there was no instance where the Benedict's solution was negative when one of

TABLE 2

Group I—Comparison of four urine tests in thirty-nine previously unknown diabetics

	Benedict's Solution		Benedict's Tablet	
	Positive —39	Negative —0	Positive —29	Negative —10
Oxidase Paper A				
Positive	28	0	27	1
Negative	11	0	2	9
Oxidase Paper B				
Positive	32	0	27	5
Negative	7	0	2	5

the other tests was positive. Benedict's solution thus appeared to be the most sensitive of the four tests employed, on the basis of this comparison.

For an estimate of the relative specificity of the tests employed, a comparison was made of the performance of the four urine sugar tests on twenty-two persons subsequently designated as "technical" false positive. Diabetes was subsequently ruled out in these persons, who were positive on one of the initial screening tests but not during the glucose tolerance test. From the data of table 3 it will be noted that the greatest number of technical false positive tests was contributed by the Benedict's solution, which was positive in twenty-one of the twenty-two persons in this category. Benedict's tablet was responsible for a smaller number of false positive reports, being positive in fifteen of the twenty-two. Both oxidase paper A and oxidase paper B proved more specific, to an equal degree, than Benedict's solution and Benedict's tablet, since the former tests designated as positive only three or four of the twenty-two persons in the technical false positive category.

TABLE 3

Comparison of four urine tests in twenty-two technical false positive reports

	Benedict's Solution		Benedict's Tablet	
	Positive —21	Negative —1	Positive —15	Negative —7
Oxidase Paper A				
Positive	3	0	1	2
Negative	18	1	14	5
Oxidase Paper B				
Positive	3	0	1	3
Negative	18	1	14	4

On the basis of the comparisons described above for Group I, Benedict's solution proved most sensitive in detecting new diabetics, albeit the least specific of the four urine tests compared. Oxidase paper B appeared to be the most sensitive of the two enzyme tests, and as specific as oxidase paper A in excluding nondiabetics.

GROUP II

As mentioned above, improved performance over that observed in the analysis described above, using early clinical trial products, was noted when a new supply of enzyme-testing products for urine sugar was employed. In fairness to these improved products, it was decided to prepare an additional comparison based upon their use. In the comparisons to be described, a single test, Benedict's qualitative solution, was employed to represent urine sugar tests which measure total reducing substances, since this test proved more sensitive than Benedict's tablet in our preliminary analysis, and sensitivity is of prime importance in a detection program.

The size of the second group studied was approximately the same as that of the first group, described above, and consisted of 3,991 persons. In addition to applicants for periodic detection tests, this group also included patients attending the Surgery and Gynecology Out-Patient Clinics, but was otherwise of the same composition as Group I. From table 1 it will be noted that 5 per cent of this group (198) screened positive to one or more of the urine sugar tests employed. This figure is higher than that observed in the first group (3.3 per cent), but this is accounted for mainly on the basis of the increased number of known diabetics found in the second group. By a coincidence, the number of previously unknown diabetics found was exactly the same (thirty-nine) in both groups.

Table 4 presents an analysis of data on the thirty-nine newly discovered diabetics in this group. It will be noted that the sensitivity of the three urine sugar tests proved to be identical, each of these tests identifying thirty-seven of the thirty-nine new diabetics. The two diabetics reported as negative by each test obviously were reported as positive by one of the other tests. This represented an improved performance of the enzyme tests when compared to the results obtained in the first group of persons tested.

TABLE 4

Group II—Comparison of three urine tests in thirty-nine previously unknown diabetics

	Benedict's Solution		
	Positive—37	Negative—2	Total
Oxidase Paper A			
Positive	36	1	37
Negative	1	1	2
Oxidase Paper B			
Positive	35	2	37
Negative	2	0	2

Table 5 presents comparative data on nineteen persons who showed a technical false positive test with one or more of the above urine tests. The Benedict's solution was relatively the least specific of the tests compared, being positive in all members of this group. Oxidase paper B was relatively the most specific test, with only four technical false positive reports. Oxidase paper A showed a somewhat higher number (seven). The groups are too small to determine whether improved sensitivity of the enzyme tests has been achieved at a sacrifice of specificity, although there is some suggestion of this in the results obtained with oxidase paper A.

TABLE 5

Group II—Comparison of three urine tests in nineteen technical false positive reports

	Benedict's Solution Positive—19	Negative—0	Total
Oxidase Paper A			
Positive	7	0	7
Negative	12	0	12
Oxidase Paper B			
Positive	4	0	4
Negative	15	0	15

DISCUSSION

The hazard of drawing conclusions from preliminary studies of newly available products is indicated by our experience of observing an inferior performance by the urine sugar enzyme tests in our first study (Group I), with an improved performance subsequently when a new supply of the test materials was employed under similar conditions in another group (Group II).

The relatively high degree of sensitivity of Benedict's solution was observed in both groups of the study, and indicates that this time-honored test is not without merit. The inconvenience of having to heat specimens tested, and the frequent false positive tests reported by this method represent its main shortcomings, although the importance of these aspects can be assessed only in relation to facilities, personnel, and funds available for a testing program. Under some circumstances this test may still provide the most economical way of finding new diabetics in view of the low cost of materials needed.

The performance of the two enzyme tests for urine sugar, oxidase paper A and oxidase paper B, in the second part of our study indicates that they are equivalent to Benedict's solution in relative sensitivity and superior to it in relative specificity. Under circumstances where urine specimens can readily be obtained and rapid testing of a large volume of specimens in a short time is desirable the oxidase papers would appear to be the tests of choice. While the costs of these products are higher than that of Benedict's solution, there would be fewer instances where time-consuming follow-up efforts would be required in cases with false positive tests. Conclusion is that for a mass outpatient department program or for office use in the detection of diabetes either of the above enzyme tests for urine sugar is superior to the conventional test using Benedict's qualitative solution.

SUMMARY

Eight thousand persons were screened for diabetes by urine tests in an outpatient department; 1 per cent were found to have previously unknown diabetes.

Comparison was made of the relative sensitivity and specificity of four urine sugar tests, namely: Benedict's solution, Benedict's tablet, oxidase paper A and oxidase paper B.

In a preliminary comparative study of 4,000 persons, using early clinical trial products, the enzyme tests for urine glucose proved less sensitive than Benedict's solution, but in a subsequent study of a similar group, employing improved enzyme test products, they proved equal to Benedict's solution in sensitivity and superior to it in specificity.

Consideration is given to the circumstances under which the above tests may be most effectively employed in diabetes detection.

SUMMARIO IN INTERLINGUA

Comparation Del Test De Benedict E Del Test A Oxydase De Glucosa Pro Le Detection De Diabete in Essayos In Massa

In un departimento de patientes visitante, 8000 subjectos esseva examinate pro diabete per tests de urina. Esseva trovate que un pro cento habeva diabete non previemente cognoscite.

Esseva comparate le sensibilitate e specificitate relative de quatro tests de sucro urinari. Illos esseva le test de Benedict a solution, le test de Benedict a tabletta, le test per oxydase a papiro A, e le test per oxydase a papiro B.

In un studio preliminari con 4000 subjectos, in le qual le productos de essayage clinic esseva usate in un forma non jam perfectionate, le tests enzymatic pro glucosa urinari se monstrava minus sensibile que le test de Benedict a solution, sed in un studio subsequente de un simile gruppo, in le qual le productos de essayage enzymatic esseva usate in un forma meliorate, le tests a enzymas se monstrava equal al test de Benedict a solution in sensibilitate e superior a illo in specificatate.

Es discutite le circumstantias sub le quales le supramentionate tests pote esser empleate le plus efficacemente in le detection de diabete.

ACKNOWLEDGMENT

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A Multiplicity of Reactions to Carbutamide (BZ-55) Therapy

Report of a Case

John A. Tulloch, M.D., Jamaica, B.W.I.

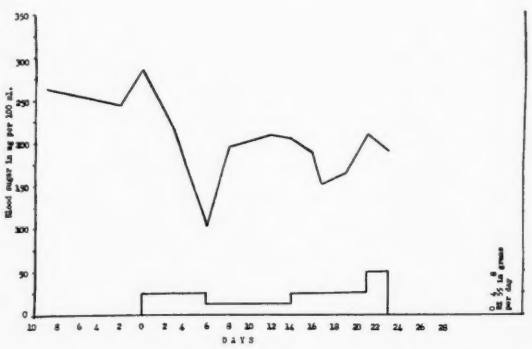
Reactions to carbutamide have been many and varied and deaths occasionally have been associated with its use (Kirtley,[1] Field and Federman[2] and Page[3]). The following case is reported because of the remarkable multiplicity of the reactions following high dosage of the drug.

CASE REPORT

J. C., aged forty years, a cultivator, was first seen as an outpatient at the University College Hospital of the West Indies on June 4, 1954, because of dimness of vision and deafness. He was found to have diabetes. His diet was assessed at that time and was found to be deficient in total calories, protein and fat (total calories estimated at 1,162, carbohydrate 230 gm., protein 29 gm. and fat 14 gm.). He could not afford to eat more. Rearrangement of his diet was discussed with him and the following was recommended—carbohydrate 152 gm., protein 36 gm., fat 36 gm., total calories 1,076. He did not return until Jan. 28, 1957, when he was admitted to the hospital, having collapsed while attempting to walk to the hospital from the country. During the preceding six months he had rarely walked because of weakness and pains in the legs. He also complained of thirst, frequency and precipitancy of micturition and loss of weight. The dimness of vision had increased and he was still deaf. He gave no family history of diabetes.

On examination he was slightly dehydrated. His weight was 130 lb. (ideal weight 149 lb.). The heart was not enlarged, the peripheral pulses were all present, the radial artery was slightly thickened and the blood pressure was 130/84 mm. Hg. Bilateral optic atrophy was present. The liver was not enlarged. There were signs of a moderately severe peripheral neuritis in his lower limbs. The urinary sugar ranged from one plus to three plus over twenty-four hours, and there was no albuminuria. Microscopic examination of the urine showed no abnormality. The hemoglobin was 12.5 gm. per 100 ml., and the total white cell count 4,400/cm. with a normal differential count. Liver function tests were not grossly abnormal apart from reversal of the A/G ratio, the serum albumin being 2.7 gm. per 100 ml. and the globulin 5.0 gm. per 100 ml. The total cholesterol was 135 mg. per 100 ml. A fasting blood sugar was 263 mg. per 100 ml. The V.D.R.L. was negative. X-ray examination of the chest showed no abnormality.

The patient was started on a 2,000-calorie, diabetic-type diet and was given vitamin B complex three times a day. On this regimen his urinary sugar (estimated six times each twenty-four hours) ranged between one plus and four plus. After seven days on the diet, the blood sugar levels during the day were: *fasting*, 245 mg.; at 10:30 a.m., 256 mg.; at 3:30 p.m., 270 mg.; and at 10 p.m., 272 mg. per 100 ml. Two days later (Feb. 7, 1957) the fasting blood sugar was 286 mg. per 100 ml. and he was started on 2 gm. of carbutamide twice daily. This dose was continued for six days, during which time the urinary sugar output decreased almost to zero and the fasting blood sugar fell (figure 1). The dose of carbutamide was therefore reduced to 1 gm. twice daily on the seventh day of therapy (February 13) but this dose did not maintain the reduction in the blood sugar level, and glycosuria ranging from one plus to four plus returned. On the sixteenth day (February 22) the dose of carbutamide was increased to 2 gm. twice daily. Again there was a temporary but less marked reduction in the fasting blood sugar (figure 1). It was therefore decided to double the dose as from the twenty-third day (March 1) and to give 4 gm. twice daily. This was done although the platelet count was 50,000/cm. on the fourteenth day and 90,000/cm. on the nineteenth day (table 1). No other toxic features had been noted.



The high dose was given for only two days. At 1 and 4 a.m. on the second night he developed weakness, "bad feelings," drowsiness, headache and sweating, and on each occasion these symptoms were relieved by the administration of 20 gm. of glucose by mouth. No blood sugar estimation was made during either attack. Similar episodes occurred once nightly for the next three nights and on each occasion were relieved by oral glucose. During the last attack the blood sugar was 202 mg. per 100 ml. prior to the glucose administration. A fasting blood sugar was 267 mg. per 100 ml. on the third morning after administration of the carbutamide was stopped.

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TABLE 1

Date	Hb. in gm./100 ml.	W.B.C. per cu. mm.	Differential white cell count: Neutrophils	Eosinophils	Basophils	Small Lymphocytes	Atypical Lymphocytes	Monocytes	Platelets per cu. mm.
30/1/57	12.5	4,400	63	2	—	26	—	9	
8/2/57	11.4	5,000	49	4	—	42	—	5	150,000
12/2/57	12.1	3,850							160,000
18/2/57									136,000
22/2/57	11.7	3,800	62	—	1	35	—	2	50,000
27/2/57	11.2	3,000	44	2	—	46	—	8	90,000
2/3/57	11.4	3,550							72,000
7/3/57	10.1	4,200	45	17	—	37	—	1	70,000
13/3/57	12.2	24,100	19	2	—	72[1]	—	7	110,000
19/3/57	9.3	24,400							90,000
20/3/57	10.0	22,850	19[2]	2	—	63	6	5	
21/3/57	9.0	8,000	47[3]	—	—	29	2	7	90,000
25/3/57	9.2	10,200	71[4]	—	—	14	8	1	
26/3/57	9.2	9,600	82[5]	—	—	8	5	5	70,000
28/3/57	9.1	8,200	44	1	—	48	2	5	70,000
1/4/57	8.9	4,900	72	—	—	26	—	2	90,000
5/4/57	9.0	5,300	68	2	—	22	—	8	70,000
10/4/57	9.3	4,700	47[6]	19	1	31		1	
12/4/57	9.6	4,200	44	25	—	28	—	3	100,000
16/4/57	11.0	5,400	29	21	—	49	—	1	80,000
18/4/57	10.5	3,800	54	6	—	38	—	2	70,000
23/4/57	11.3	5,300	43	1	—	53	—	3	170,000
3/5/57	12.0	6,750	53	3	—	44	—	—	160,000

[1] A number of lymphocytes were atypical.

[2] Two per cent band form neutrophils and 3 per cent metamyelocytes, three polychromatophilic normoblasts per 100 cells.

[3] Seven per cent band forms of neutrophils, 7 per cent metamyelocytes, 1 per cent myelocytes, four polychromatophilic normoblasts per 100 cells.

[4] Six per cent band forms of neutrophils.

[5] Three polychromatophilic normoblasts.

[6] One per cent band forms of neutrophils.

A total of 87 gm. of carbutamide was given in twenty-four days. Sulfonamide blood levels were not measured.

On the day after carbutamide administration was discontinued (March 3) the patient's temperature rose to 101.4° F. and by the following day was 102.4° F. A few fine crepitations at the end of inspiration were detected in the left axilla and, as it was considered that he might be developing pneumonia, treatment with crystalline penicillin, 500,000 units, six hourly, was begun. This was given for three days and was followed by procaine penicillin, 600,000 units daily for two days. The pulmonary signs disappeared and the temperature fell, but only temporarily. It rose again gradually on the day after the penicillin was stopped (March 9). A few pulmonary signs reappeared in the left axilla on March 12. Procaine penicillin, 600,000 units daily, was readministered that day but was discontinued again after three days as the clinical diagnosis of pneumonia was considered to be doubtful since there was no X-ray evidence. In addition, the temperature was not influenced by the penicillin, and the white cell count on March 13 had risen to 24,100/cm. with 19 per cent of polymorphs and 72 per cent of small lymphocytes.

Subsequent developments were as follows. On March 14 (twelve days after ceasing carbutamide) the patient's skin looked coarse and reddish and his face was slightly puffy. A shallow ulcer had developed on the left side of the nose. The fauces showed the presence of yellowish exudate. Enlarged lymph glands were present in the cervical, inguinal, axillary and supratrochlear groups. The spleen and liver were not palpable and there was no hepatic tenderness. The urine contained a trace of bile and a trace of urobilinogen. On microscopy there were frequent granular casts. Liver function tests next day (March 15) showed a rise in serum bilirubin to 3.7 mg. per 100 ml. (1 minute) and 5.5 mg. per 100 ml. (total), a fall in the cholinesterase to 0.32 units and a rise in the alkaline phosphatase to 24 King Armstrong units. Clinical jaundice was apparent that day and increased in depth for about one week. On March 19, the serum bilirubin was 8.7 mg./100 ml. (1 minute) and 18.0 mg./100 ml. (total) while the cholinesterase was 0.4 unit and the alkaline phosphatase 30 units. The thymol turbidity was also abnormal, 6.4 units. Thereafter the serum bilirubin fell but the thymol turbidity and alkaline phosphatase levels continued to rise, reaching a maximum on March 26 of

16.1 and 50 units, respectively. These two tests returned toward normal very slowly and were slightly abnormal on May 3 (thymol turbidity 6 units, alkaline phosphatase 18 units) just prior to his discharge from hospital.

Accompanying the hepatitis and the lymphadenopathy were an exfoliative dermatitis and changes in the blood picture particularly involving the white cell series. The changes were a rise in the total white count (24,100 per cm. on March 13) with a relative granulopenia, a marked lymphocytosis and the appearance of atypical mononuclear cells. This very abnormal blood picture persisted for eight days. A few normoblasts and primitive granulocytes were noted in the peripheral blood and there was a late, brief eosinophilia. A mild anemia (Hb. 8.9 gm. per 100 ml.) also developed.

The exfoliative dermatitis (with which the second rise in temperature was probably associated) became apparent on March 14. Cortisone, 200 mg. per day, was begun on March 16, and within thirty-six hours the temperature was normal. The hyperemia and edema of the skin steadily lessened, and by March 19 the skin had begun to peel from the face and chest. The dose of cortisone was reduced to 100 mg. per day on March 20 and 75 mg. per day on March 22. This second reduction was associated with an immediate return of fever. The cortisone dosage was therefore increased to 150 mg. per day on March 24 and forty-eight hours later the temperature was again normal. This dose was maintained until March 30 and the cortisone was then gradually discontinued over the next nine days. By April 1 the lymph glands had begun to regress in size, and on April 8, only a few small cervical glands were to be felt.

On April 15, the face was noted to be swollen again and the skin was slightly hyperemic and itchy. Benadryl, 50 mg. three times daily, was given without improvement, and although there was no fever, cortisone was restarted on April 18 and given for thirteen days. This produced a prompt regression of the skin changes and there was no further recurrence. There was no associated glandular enlargement and no change in the blood picture.

No specific therapy for the diabetes, apart from diet, was given during the first four days after administration of the carbutamide was stopped. On March 7 the diet was increased to 2,500-calories as he complained of hunger. Thereafter 20 to 30 units of Insulin Zinc Suspension (Lente) were required per day to control the diabetes. When the hepatitis developed he was given a diet high in protein and carbohydrate (carbohydrate intake was not accurately measured) and when the cortisone was started on March 16, he was changed to soluble insulin given once or twice daily as indicated by the degree of glycosuria. Twenty to forty units were required per day until March 23 when the glycosuria increased and up to 105 units of soluble insulin per day were required. With the improvement of the hepatitis a 2,000-calorie diabetic type diet was restarted on April 1 and his insulin requirements fell gradually to 20 units of I.Z.S. Lente per day. During the latter part of the second course of cortisone the insulin requirement rose to 60 units of I.Z.S. Lente per day and then fell again to 20 units per day prior to his discharge on May 6.

He has since disappeared into the country, and as he is homeless, penniless, somewhat deaf, of low intelligence and has impaired vision, it is unlikely that his diabetes is still controlled. He can inject himself but cannot measure the dose of insulin.

DISCUSSION

This case shows a number of interesting features: (a) the initial prompt response to 4 gm. of carbutamide per day, not maintained when the dose was halved and only partially reproduced when the 4 gm. per day was renewed; (b) the thrombocytopenia during the later stages of the carbutamide administration; (c) the apparent nocturnal hypoglycemic attacks after two days of 8 gm. per day and the persistence of such attacks for three nights in spite of the cessation of therapy; (d) the multiplicity of other toxic effects developing after administration of carbutamide had ceased.

Sulfonamides have the capacity to combine readily with plasma proteins, thereby becoming antigenic. It is known that although sensitivity reactions such as fever may appear about the seventh or eighth day of therapy, reactions to the sulfonamide drugs may tend to be proportional to dosage and duration of therapy (Alexander[4]). Continued administration may allow the appearance of allergic manifestations during a first course of therapy, but these may not develop until several days after the drug has been stopped. The patient herewith reported received 87 gm. of carbutamide in twenty-four days. Thrombocytopenia developed during the latter half of therapy and was not aggravated by restoring the daily dose of carbutamide to 4 gm. for seven days or by increasing it to 8 gm. per day for two days. Six weeks elapsed after withdrawal of the carbutamide before a consistent increase in the platelet count was recorded. The fever noted on the day following cessation of therapy may have been a drug fever as the evidence of pneumonia was inconclusive. The subsequent toxic reactions of exfoliative dermatitis, lymphadenopathy and lymphocytosis, appearance of a few abnormal red and white cells in the peripheral blood, toxic hepatitis and mild anemia are probably all related to the carbutamide administration but the patient did receive penicillin in two short courses just prior to their onset (March 3-7 and March 12-14). It is unlikely, although possible, that the penicillin produced these several effects as they had begun to appear during the second course of treatment. In addition, arthritis or arthralgia (both absent in this patient) are common in severe penicillin reactions but occur infrequently with sulfonamides. Another possibility is that the procaine in the penicillin was causally related to the toxic features. Cross reactions between procaine and sulfonamide drugs are known to occur[4b] and it is therefore possible that the procaine triggered off the severe systemic reactions in an already sensitized patient. Lymphadenopathy has been described following procaine amide administration.[5] On

the other hand anemia, hepatitis and exfoliative dermatitis are probably more liable to occur with carbutamide than with procaine. Development of hepatitis may have been potentiated by his prolonged subcaloric diet prior to admission to the hospital and in particular by the severe protein deficiency. It seems reasonable to associate these numerous toxic reactions and the persistence of the thrombocytopenia with the administration of one drug—carbutamide, but the possibility of a cross reaction with procaine cannot be excluded.

The apparent nocturnal hypoglycemic features exhibited by this patient after two days on the dosage of 8 gm. per day are of considerable interest, and their recurrence between 1 and 3 a.m. on three successive nights is more unusual. Each attack was promptly relieved by administration of glucose. Early in the last attack the blood sugar was 202 mg. per 100 ml. This clinical picture of "hypoglycemic" symptoms at elevated blood sugar levels has been seen in one other Jamaican patient who was also receiving 8 gm. of carbutamide per day,[6] and who showed two types of attack—one which responded quickly to glucose administration and a prolonged attack not associated with low blood sugar levels and not influenced by administration of a large amount of glucose both orally and intravenously. This patient also exhibited such attacks after cessation of the carbutamide. The exact nature of these episodes is not as yet clear, but undoubtedly there must be interference with cellular utilization of glucose when the blood sugar is below some critical level. The duration of the "hypoglycemic" attack and the promptness of its relief probably reflect the extent of the interference with cellular metabolism. That these attacks are directly related to the high oral dosage of carbutamide after prolonged administration at a lower level seems indisputable. Reactions resembling hypoglycemia occurring in dogs have been reported by Sirek et al.[7]

It is known that carbutamide interferes with the activity of certain liver enzymes—cytochrome oxidase is inhibited,[8] insulinase activity is decreased[9] and glucose-6-phosphatase activity is decreased.[10,11] A generalized blocking of cellular utilization of glucose at higher blood concentrates of carbutamide than are commonly achieved seems probable. The interference is usually reversible and can be overcome by raising the blood level of glucose. It is unlikely that there is any connection between the "hypoglycemic" attacks and the many toxic reactions shown by this patient unless the factor or factors initiating the attacks also altered the response of the cells to the sulfonamide—protein antigen.

SUMMARY

The case of a diabetic adult male who exhibited a number of serious toxic reactions to carbutamide administration is reported. The findings included thrombocytopenia, fever, lymphocytosis, generalized lymphadenopathy, exfoliative dermatitis, hepatitis and the development of a secondary anemia. Recovery followed administration of cortisone. Delayed "hypoglycemic" episodes were associated with administration of high dosage of the drug.

SUMMARIO IN INTERLINGUA

Un Multiplicitate De Reactiones A Therapia Con Carbutamido (BZ-55): Reporto De Un Caso

Es reportate le caso de un adulte masculo diabetic qui exhibiva un numero de serie reactiones toxic al administration de carbutamido. Le constatationes includeva thrombocytopenia, febre, lymphocytose, lymphadenopathia generalisate, dermatitis exfoliative, hepatitis, e le disveloppamento de anemia secundari. Le patiente se restabliva post le administration de cortisona. Retardate episodios "hypoglycemic" esseva associate con le administration de alte doses del droga.

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Special Article

Life Insurance for Diabetics

J. E. K. Kennedy, Atlanta, Georgia

There are two distinct sides to the advice and guidance you give to diabetics in the course of your doctor-patient relationship. There is first what might be termed the physical side—what his medication should be, what he should do, what he should not do. Then there is the important aspect of your treatment related to his mental attitude. An unworried patient is a better patient—for you, and for him—than one who is a prey to fears and apprehensions. So you try to develop in him an optimistic and philosophical attitude towards a condition of health which might otherwise tend to depress him. You explain to him how, with proper care and appropriate compensations, he can expect to live virtually a normal life. What is a normal life? Certainly on the economic side, a vital part of it is earning a living in a normal way for himself and any dependents he may have. And what is life insurance for the diabetic, but simply a means of insuring his economic value—that normal earning power which you are at pains to impress upon him will be his. Clearly, then, the ownership of life insurance is a necessary and normal part of modern living—a part long denied, but happily now increasingly available to him. Anything affecting your patient's life and well-being has some relation to your own objectives for him, and on this premise examination of his position with regard to insurance seems amply justified.

In my office library is a life insurance textbook written in 1940. It was considered to be authentic when it was published. When I started preparing my notes for this talk it occurred to me to see what it said about diabetes. There was but one sentence: "Diabetics are not considered insurable even if under adequate medical supervision." Now that was in 1940! The developments in extending life insurance service to diabetics, therefore, have occurred mainly in the last ten years. It is still definitely experimental. First, a few companies cautiously opened the door, then others gradually followed suit, encouraged by the growing—but still relatively limited—volume of experience data.

When we look at the science of underwriting we find that there are two separate types of factors which enter into the appraisal of any particular class of risk. First, there are the factors which are present in every such case, and second, there are those many and diverse factors which apply to each individual risk in varying combinations. Two of these ever-present factors have been important areas of gradual development in underwriting diabetic risks. The first of these is the factor of age. Initially the age limits of acceptability were narrowly restricted to the middle ages—the thirties and forties. This range has gradually widened, though more hesitantly downward than upward. Today the acceptance of risks as young as twenty is fairly commonplace but rare below that age. At the other end acceptance runs as high as seventy.

The second area of development relates to the severity of the disease itself, as measured by the necessary daily insulin dosage. Here again we have seen a gradual evolution from the early acceptance of only the mildest cases, to a fairly common limit of 50 units of insulin daily—some companies going as high as 75 units.

Here then we have the two primary standards of acceptability. A high percentage of your patients will be eligible on both counts and if other individual factors do not too seriously cloud the picture they can get life insurance today. They will not get standard rates, of course, so let us now take a look at the justification for imposing special terms.

A life insurance premium increase, or rating, as it is called, is a mathematical estimation of an increased risk of death. Among those suffering from diabetes—no, let me take that expression back, for it runs counter to the philosophy which you rightly seek to impart to your patients. A man may suffer from arthritis or a toothache, but he does not *suffer* from diabetes. Instead—if he heeds your advice—he simply learns to *live* with it. So, to rephrase my earlier sentence, among diabetics statistics show a substantial excess mortality as compared with figures for the general population.

In the relatively short span of years that life insur-

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ance has been issued to diabetics there has not been sufficient total exposure to provide material for an intercompany survey. Such an investigation must be based upon a great many lives and over a long period to justify a widespread application of its conclusions to underwriting practices. This will come in time, of course, and will be a valuable guide to all companies in extending life insurance service to what is an appreciable segment of the population.

Meanwhile, among surveys of more limited scope, perhaps the most authentic is one based on the experience of the Joslin Clinic during the five-year period from 1947 through 1951. The subjects were patients first coming under their observation from 1930 through 1951. From this investigation a table was compiled illustrating, at the various ages, first, the expectation of life and, second, the mortality rate year by year. Let me just very briefly indicate the trend of the figures. For example, at age ten table 1 shows diabetics with a life expectancy of 44.3 years compared with the 1949-51 general U.S. white population expectation of 61.5 years.

TABLE 1*

Age	Diabetics Years	General white population Years
10	44.3	61.5
20	36.1	51.9
30	30.1	42.5
40	23.7	33.3
50	16.9	24.7
60	11.3	17.2

You will observe that through this table the diabetic's life expectancy is a little more than two thirds that of the general population.

As shown in table 2 there is a still greater contrast percentage-wise in the mortality rate. At age ten in the general population the yearly mortality rate is 0.5 per thousand, while the Joslin statistics brought out a rate of 2.6 per thousand.

Here are a few age comparisons.

TABLE 2*

Age	Diabetics Per thousand	General white population Per thousand
10	2.6	.5
20	8.0	1.2
30	15.2	1.5
40	12.2	3.2
50	21.6	7.9
60	49.8	18.7

Here you see among children and young adults a mortality rate running five to ten times that of the general population with smaller, though still significantly high, ratios at the middle and older ages.

A review of the actual causes of death would take us so much into the realm of your own familiarity that, coming from me, it would be something like carrying coals to Newcastle. However, not as a concession to sentiment —for the old city of Newcastle happened to be my birthplace—but simply to round out my references to the particular study from which I have quoted, let me just add these percentages. Of the total deaths studied, 33.4 per cent resulted from coronary artery diseases, with other heart diseases bringing the total in this category up to 48.7. The other principal causes were vascular lesions of the central nervous system 13.1 per cent, cancer 10.1 per cent, and nephritis 9.9 per cent.

This is the type of data on the basis of which the life insurance industry is trying to extend its services to diabetics. It is admittedly inadequate for as yet it is limited in scope. By way of further example, since it is only some thirty-six years since insulin treatment began, we are only now entering the stage where study can be made of the first generation of childhood diabetics surviving in any number through the middle range of ages. For this contrast with the earlier excessive mortality among diabetic children, the world owes much to our distinguished visitor from Toronto, Dr. Charles H. Best.

At this point I would like to go back to an earlier brief reference I made to a special characteristic of diabetes, namely, the unique extent to which the future health of the diabetic patient is governed by factors coming within his own control. This very fact has contributed in an important degree to the hesitation of insurance companies in entering the field of diabetic risks. Unlike many diseases where there is experience data giving a clear guide to their expected progression, the patient with diabetes may, by sensible adherence to his appropriate regimen, hold his impairment stationary through the years—or by his failure in that regard, he may accelerate its seriousness. In other words, the factor to be predicted here is human nature—than which there is hardly anything *less* predictable. The diabetic with an established record of good regulation and, for him, sane living, looks like a good measurable risk—but will he stay that way? Let his wife run off with his best friend or some serious business reverses hit him and he may jump right of his well-defined track. Since the crystal ball has no place on the desks of our actuaries it is not too hard to understand the caution exercised in approaching this particular field of underwriting.

Incidentally, the development of oral medication of the hypoglycemic type may well affect the underwriting

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of diabetic risks. For those diabetics suited to this type of treatment, the physical challenge of sustained regulation is certain to be reduced when the daily injection process is eliminated. It may then follow that the hazard of interrupted or discontinued regulation may be diminished, and the lowered odds of this happening be reflected in premium rating calculations. It will take time, of course, but this is an interesting speculation.

The task of our medical officers and actuaries is to evaluate excess mortality and its relationship to the various other factors having a bearing on classifying the individual risk. First, a limit of acceptability has to be established, beyond which the risk must be rejected. Then, short of that line, there may be several graduated classifications with a corresponding graduation in the insuring terms offered. Perhaps a good way to look briefly at the factors entering into this classification process would be to see what were the causes of rejection in a typical group of applications from diabetics. This particular survey indicated an acceptance ratio of roughly 75 per cent. Some 27 per cent of the actual rejections resulted from the underwriter's conclusion that adequate supervision was lacking. This would include weight regulation. It is obviously important to his insurance eligibility that the patient visit his doctor regularly and that he exercise the greatest self-discipline as to regularity of diet, exercise and administration of insulin. Within reasonable limits as to his physical condition otherwise, the first and in some respects the most significant test of his insurability is a substantiated record of consistently living on a regimen suited to his disease. Furthermore, as already stressed, the diabetic is in the unusual position of having this primary test related to something coming within his own control.

In this same study, some 23 per cent were rejected due to abnormalities in electrocardiograms, or heart impairments. In 15 per cent of cases the reason was elevated blood pressure; 8 per cent of the declinations were due to habits, 7 per cent to excessive insulin dosage, 20 per cent to a variety of miscellaneous reasons.

It is only to be expected that there should, at this early stage, be some variation in underwriting practices. The companies fairly generally will now accept most risks up to an estimated mortality rate of 500 per cent of normal. However, they may differ in their precise appraisal of a particular risk and in the terms which they consider appropriate. The increase in premium for an impaired risk is not necessarily proportionate to the expected increase in mortality. As a simple illustration consider a class of risk where the expected mortality is 200 per cent of normal. Since double the normal number of claims will be expected, the premium would have to be more or less double the regular premium, on *Term* insurance. However, with Whole Life, Limited Payment Life and Endowment plans, the amount at risk—represented by the difference between the face amount of the policy and the cash value—decreases continuously throughout the lifetime of such policies. Now the mortality costs are based only on the amounts at risk, and so the premiums for impaired risks on these plans will seldom be as much as double the standard premium even where the expected mortality is three or four times the normal rate.

Up to this point we have taken a look at diabetes with the completely impersonal eye of an organization which must study diabetics as a group. By reviewing some data on comparative mortality, causes of death within the group, and reasons for insurance rejections, we have in the process seen what health and other factors are important from an insuring standpoint.

Here are some fairly representative company attitudes. First, diabetics are not generally acceptable until their impairment has been stabilized by the use of insulin or diet for a period of from six months to two years. Second, very small policies are discouraged due to the expense of investigating and underwriting. At the other extreme, maximum risks are also limited, depending on the degree of the impairment. All companies are extremely cautious in their approach to any question of overweight—not just because of its own direct significance—but because it may be indicative of poor supervision or poor cooperation on the part of the patient. A combination of elevated blood pressure and diabetes is, of course, unfavorable, but if there are no other unfavorable factors those with slightly elevated blood pressures will generally be accepted on some terms. Another fairly general stand is that the fasting blood sugar should be consistently below 150 mg. Readings substantially over that level would indicate poor control, and generally result in rejection. Evidence of renal disease is looked upon most unfavorably and this would also apply to any history of recurrent infections. Another important point is the age at onset of the disease as distinct from the age at application. Practices vary in this regard, some companies being unwilling to insure any lives where the original onset of the disease was prior to age twenty, while others take a more liberal attitude. Finally, in connection with alcoholic habits, anything more than the most moderate use could again be indicative of poor control and prompt rejection.

We have pretty well covered the considerations involved in the reception of an application by a diabetic

for life insurance. If the applicant is not too young, the disease not too severe, and the case not too complicated by other factors, the likelihood is that life insurance is obtainable upon some appropriate basis. You will recall my earlier quotation from a survey of such applications, indicating an acceptance ratio of about 75 per cent. Now as to the terms offered to the successful applicants, I believe I would be right in saying that a very high percentage of the ratings offered would be within the range of an additional $10.00 to $20.00 yearly, per thousand. There will be instances of ratings both below and above this range, but they will be in the minority.

While my references have been to male lives, they would also, in general, apply to females. Of course their reasons for applying for life insurance are different, but they are nonetheless important, particularly from certain tax standpoints. An unusual reason was one given by a widow when she was handed a check for her husband's life insurance. On being asked whether she wouldn't like to buy some herself she replied, "You know, I think I should. My husband had such good luck with his."

I want to leave the more or less technical aspect of the subject and make a few observations upon what I conceive to be your opportunity, and perhaps even your responsibility, as a part of bettering and enriching the lives of your diabetic patients. I do not think I am being presumptuous in using the term "responsibility" for I speak as one who has for some thirty-one years devoted himself to bettering the economic health of his fellow man.

It has been my experience—just a very few times in many years—to meet a rare type of individual: the man who "doesn't believe" in life insurance. Usually this man will have his house insured—and his furniture—and, of course, his automobile. Ten to one he has a hospitalization policy, too. What does this add up to? It simply means he will only pay for protection against losses he, himself, would suffer. This is rough on his family, but on the man, himself, I would waste little time or sympathy. There is another type encountered much more frequently, unhappily, and for him I have a world of sympathy. I refer to the man with a natural depth of unselfish love for his family and a deep concern for their security, but who is debarred from translating those sentiments into protection—because he cannot get life insurance. There must be times when such a man suffers agonies of apprehension.

Many such men walk in and out of your offices. Many such men are accustomed to listening attentively to your words of help and guidance. Among them must be many who are eligible for life insurance under today's standards but who are unaware of this. Here, then, is your opportunity to do them a real service. And—if I am correct in my earlier premise that anything tending to better their lives and reduce their worries and tensions has a relation to your own objectives for them—might we not go further and describe this even as your responsibility. Just an offhand remark—perhaps some casual comment about the way life insurance companies seem to be modifying their attitudes towards diabetes—or a remark that you hear life insurance is becoming increasingly available to them—is all that would be needed. They will take it up from there, if they are concerned and interested. You may thus bring about a significant turning point, insofar as their emotional and economic lives are concerned. Then, too, I submit that in your dealings with future new diabetic patients, when you are reviewing the many aspects and significances of this new reality with which they find themselves confronted, some reference to the possibility of their later re-acquirement of eligibility for life insurance would be appropriate and helpful.

Now let us assume for the moment that you find yourself in agreement with this reasoning as to the justification for volunteering some comment on your patient's insurance status. Then next is this question. Would any reference to life insurance, and the obvious fact that the patient would be charged special rates, be harmfully in conflict with your effort to have him adopt the philosophy of "living a normal life?" I do not think this must necessarily be so. In telling him how a virtually normal life may be lived if he adopts and maintains those regulations which you prescribe, you are presenting an outlook for him personally, not for diabetics as a class. In fact you are, by inference, contrasting the outlook of those particular diabetics who have enough balance to stay unwaveringly on their proper regimen with the outlook of those who have not. It is a simple question of averages as far as life insurance is concerned. Your patient cannot help being in a general class which, on the average, requires special rates—but he can largely determine by his own conduct whether he will turn out to be in the upper or lower stratum of the class in which he falls. It's as simple as the comparison with fire insurance. The man with a frame house, paying a higher premuim than neighbors with stone houses, is the victim of what you might term a statistical generality, but he has no cause either to feel resentment on the one hand or greatly increased worry on the other.

I suppose some natural instinct makes us rebel against paying more for something than the other fellow does. I have encountered men who would leave their families

without life insurance protection rather than pay some modest rating. It's really a matter of getting the right slant on it. Here again you have an opportunity to do something beneficial for your patient. In your role of advisor you can help condition his mind to the acceptance of premium ratings as a completely impersonal adjustment justified by an average, rather than an individual, increase in risk.

As a concluding point in this review of your relationship to your patient's life insurance problem, let us look at your part when he actually submits an application. Ranking well up in importance with the report from the Company's regular examiner will be the special questionnaire which they will ask you, as his medical advisor, to complete. Apart from the specific factual answers this will call for, this inquiry seeks to determine the applicant's attitude. As emphasized earlier, one of the most significant factors to the Company is the applicant's record, as seen by you over a period, in the matter of cooperation and self-discipline.

Nothing could be more helpful in the interests of your patient than your special care in handling this. If his record has been good you should go out of your way to make this clear.

EDITORIAL

ORAL HYPOGLYCEMIC AGENTS AND THE CONTROLLED CLINICAL STUDY

Some time ago an elderly patient came back to the Diabetes Clinic at the Boston City Hospital and proudly announced that he no longer needed his 35 units of insulin daily, having decided instead to reaffirm his faith in Christian Science and to renounce the syringe and needle. When his urine sugar was tested, it was negative, and his blood sugar was 82 mg. per cent. Thereafter, his control continued to be good without insulin, and he promptly handled his only lapse by writing a letter to his practitioner. Another diabetic in the same clinic, a young man of thirty-one, discontinued his usual 50 units of insulin daily and returned to the clinic four months later with sugar-free urine and a blood sugar of 132 mg. per cent. At the same time, he had gained twenty pounds.

With such a background of experience, clinicians interested in diabetes should examine with great caution any new drugs or methods of treatment lest they be greeted with undue enthusiasm, followed by an overreactive depression. Before the true place of any new therapy can be properly assessed, cautious appraisal is in order. At times we have expected too much of the new. A good example was the early disappointment with Protamine insulin because it could not control most moderate and severe diabetics when given alone. It was only after it was supplemented with regular insulin that it proved itself to be a tremendous contribution to the therapy of diabetes.

Similar high-low peaks of enthusiasm have occurred in the treatment of complications of diabetes, especially neuropathy, retinopathy, peripheral vascular disease, and in diabetes and pregnancy. Indeed, the variety of treatment for these conditions indicates the lack of a specific therapy. In many instances, a controlled study would have given a truer picture earlier, and cleared the way for further investigation. For example, the role of hormones in pregnancy could have been evaluated and truly assessed years ago by a "double blind" study such as the English have undertaken.[1]

As clinicians, it is easy for us to transmit enthusiasm to our patients, and this is especially true in the control of mild diabetics of the older, obese group, many of whom could be adequately controlled by diet and weight reduction alone. With the enthusiasm engendered by a new pill for diabetes, it is not surprising that a patient will make a more earnest attempt to become sugar free and to escape from daily insulin injections. He would be less tempted to "reach for a sweet" and would be much more cooperative as far as his diet is concerned. Another factor making it difficult to evaluate a new agent for diabetes is the known ability of mild diabetics of the older age group to get along well for long periods when insulin is omitted. For these reasons, a double blind study has obvious advantages.

Such a study was carried out in the clinic at Boston City Hospital.[2] In this study, thirty-two patients were seen at weekly intervals. They were given a pill which was either tolbutamide or an indistinguishable, similar tablet composed of dicalcium phosphate. Evaluation of control was made before the code was broken.

Degree of control was graded as follows.

Good control: blood sugar values from 60 to 150 mg. per 100 ml.; sugar tests from 0 to +, never more than ++.

Moderate control: blood sugar values from 150 to 200 mg. per 100 ml.; sugar tests from 0 to +++.

Poor control: blood sugar values over 200 mg. per 100 ml.

Of the thirty-two patients studied, twenty-six (81 per cent) had better control when on tolbutamide than when on placebo, while in six patients (19 per cent) there was no difference. In no case was control better during the placebo period. Tolbutamide produced good control in nineteen cases, moderate control in ten cases, a total of twenty-nine cases or 91 per cent having adequate control. However, during the placebo period, seven patients had good control and thirteen had moderate control, a total of twenty, or 63 per cent having adequate control. Of special interest was the fact that good results were obtained during the first week on placebo administration when it was given, by chance, *before* tolbutamide. In addition to the known hypoglycemic effect of tolbutamide, this study demonstrated a definite placebo effect which must be taken into consideration in evaluating a new agent. Some of the hypoglycemic effect of tolbutamide may therefore appear more impressive initially than it really is because of this effect. Some of the later failures, after several months on tolbutamide, may be due not to acquired tolerance to the drug, but rather to the possibility that tolbutamide was not really effective in the first place, and actually was very little more effective than placebo.

The controlled clinical trial is not new. Lasagna[3] quotes the following historic experiment: "'. . . I took twelve patients . . .(with) scurvy. . . . Their cases were as similar as I could have them. . . . They lay together in one place and had one diet common to all. Two of these were ordered each a quart of cyder a day. Two others took twenty-five drops of elixir of vitriol three times a day upon an empty stomach. Two others took two spoonfuls of vinegar three times a day. . . . Two of the worst patients were put upon a course of sea-water. Of this they drank half a pint every day. Two others had each two oranges and one lemon given them every day. The two remaining patients took an electuary recommended by a hospital surgeon made of garlic, mustard, balsam of Peru and myrrh. The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons; one of those who had taken them being at the end of six days fit for duty. The other was the best recovered of any in his condition and was appointed nurse to the rest of the sick.'

"The experiment was started by James Lind on May 20, 1747."

The search for new oral hypoglycemic agents is resulting in the development of new compounds and a second look at old ones. In a report by Reid, MacDougall and Andrews,[4] from Glasgow, aspirin was found to have a beneficial effect on a diabetic patient in whom it was administered for acute rheumatism. A similar hypoglycemic effect was observed in seven subsequent diabetics without rheumatism. The dosage of 5.0 to 8.0 gm. aspirin daily was enough to give high levels of blood salicylate and frequent tinnitus, deafness, and occasional nausea and vomiting. There is nothing in the paper to indicate the severity of the diabetes, since previous insulin requirement, if any, is never mentioned. The authors concluded, "If there is a genuine need for an oral compound to control diabetes mellitus, aspirin has an obvious advantage over the sulphonylureas, in that it may be given for prolonged periods without risk of agranulocytosis." Actually, agranulocytosis from tolbutamide is an extremely rare finding, while tinnitus, deafness, and gastrointestinal symptoms are commonly observed when salicylates are administered in this dosage range. One can not help wondering how much of the apparent improvement in these aspirin-treated diabetics was associated with poor food intake as a result of salicylate side effects, since this is not mentioned. The picture is further confused by the fact that Gross and Greenberg[5] (quoted by the British authors) report no consistent blood sugar effect of salicylates, inasmuch as this drug has also been reported to cause hyperglycemia and glycosuria. Even if aspirin were effective in lowering the blood sugar, nausea, tinnitus and deafness would be too high a price to pay for control of the mild diabetic. Better by far for our patients if these unpleasant symptoms were a signal of poor control!

In summary, the effectiveness of tolbutamide in the milder, adult-onset diabetic is well established. Unlike aspirin, its lack of toxicity and unpleasant side reactions justify its continued use. However, adult-onset diabetics have a good supply of endogenous insulin, and can often get along well after discontinuing insulin injections, especially if they adhere to a diet and lose weight. They are also susceptible to suggestion, as indicated by their satisfactory placebo response. Awareness of these facts must be included in a consideration of any controlled clinical study of oral hypoglycemic agents. Perhaps we should speak of net effectiveness (apparent effectiveness minus placebo effectiveness) of

these agents. Measured in this way, tolbutamide is definitely effective, but not as much as would appear initially.

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Carl H. von Noorden
1858-1944

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Carl H. von Noorden was born in Bonn, Germany, Sept. 13, 1858. His father, C. v. Noorden, was professor of history at German universities. After an excellent education in different schools ("Gymnasiums") in Germany the son pursued university studies, first in philosophy, mathematics and law; but he soon changed over to medicine at the universities of Tübingen, Leipzig and Freiburg. He was graduated a doctor of medicine from Leipzig. He became an assistant at the physiological institute of the University of Kiel, later assistant at the medical clinics of the universities in Tübingen (Professor Jurgensen), Giessen (Professor Riegel) and finally in Berlin (Professor Gerhardt). Von Noorden's researches and teaching abilities were recognized by his admission to the medical faculty of Giessen as "Privatdozent." Later he was appointed professor at the medical faculty of the University of Berlin. In 1892 he accepted a call to direct the municipal hospital in Frankfurt am Main. He headed the department of internal medicine and in addition operated a private hospital for diabetes and dietetic treatment. In 1906, he accepted a call as director and chief of the First Medical Clinic of the University of Vienna. He resigned from this position in 1913 and returned to Frankfurt in order to direct his private hospital there. But in 1929 he accepted once more a call to Vienna as head of a division for therapy and research in metabolic diseases at the municipal hospital of Vienna. He died in Vienna on Oct. 26, 1944.

This curriculum vitae shows that von Noorden's career was unusually successful. Moreover, many honors, such as decorations, titles and honorary diplomas from many countries, were bestowed on him. He declined many other calls to important positions in Germany as well as in other countries. He was an outstanding scientist, world famous physician, efficient organizer and an excellent teacher. His field of research encompassed metabolic and gastrointestinal disease, the science of nutrition and diet therapy. His productivity as author of textbooks and monographs is astounding: *Textbook of the Pathology of Metabolism* (1893); *Diabetes and Its Treatment* (1895, eighth edition, 1927); *Chlorosis* (1897); *Obesity* (1900); *Clinical Treatise on the Pathology and Therapy of Disorders of Metabolism and Nutrition* (1903-05); *Handbook of the Pathology of Metabolism* (with other authors, 1906); *Disease and Marriage* (with Kaminer, 1916); *Handbook of Nutrition* (with Salomon, 1920); *Clinic of Intestinal Diseases* (1921); *Diarrhea and Constipation and the Principles of Their Treatment* (1922); *Manual for Diabetics* (with Isaac, 1923); *Diseases of the Intestinal Tract, the Pancreas and Peritoneum* (1923); *Special Dietetics of Diseases of the Stomach* (with Salomon, 1929); *Old and New Problems of Nutrition* (1931).

Besides these, he published much research on metabolic and intestinal disease and on dietetic therapy in diseases of the kidneys and circulation. His textbooks also contain many valuable observations in these fields. Famous was his oatmeal diet for the treatment of diabetes before the era of insulin. Von Noorden found that oatmeal with butter taken as the only food in a certain

dietetic sequence improved the tolerance of severe diabetics and lowered the danger of acidosis. Later research showed that the oatmeal diet raised the threshold of the kidneys for excretion of glucose, and thus carbohydrate is retained and metabolized.

In addition to his extensive research and literary activities von Noorden carried on a huge private medical practice. Patients came to him from all over the world. He was also called to consultations in countries throughout the world. Unlike many specialists of internal medicine who concentrate on diagnosis, he devoted much time to therapy. He knew human nature and its different reactions to morbid conditions. His predecessor at the First Medical Clinic in Vienna, Nothnagel, coined the sentence: "Only a good man can be a good doctor." Von Noorden added the dictum: "Only a good knower of man can be a good doctor." He did not regard the specialist of internal medicine as solely a "diagnostician." One of his pronouncements was: "In internal medicine, diagnosis is skill, therapy is art."

Von Noorden was an outstanding organizer and an excellent teacher. The author of this biography was von Noorden's assistant and considered himself fortunate to be able to watch closely his activities. The First Medical Clinic of the University of Vienna was a famous teaching institution founded and headed more than 100 years ago by Josef Skoda. The Viennese medical faculty and the Austrian government were eager to call an outstanding scholar to be chief and finally appointed von Noorden. Von Noorden accepted the call with the stipulation that a new building with all modern facilities should be built. Von Noorden had many conferences with the architects and government officials during the construction, and the author, who attended some of the negotiations, admired von Noorden's expert knowledge and energetic insistence on important improvements. This building, even at the present (fifty years later), is one of the most sumptuous but at the same time practical structures for teaching and research in internal medicine. There were 160 beds all free of charge and, if necessary, a patient could be kept for months or even years for research and teaching purposes. Ample laboratories with complete modern equipment were provided. The chemical laboratory had space for more than thirty workers. There was a big X-ray department, a completely equipped physical therapy section, a separate diet kitchen, and a kitchen for teaching dietetic cookery. A spacious auditorium and a well-stocked library completed the clinic.

Thus, perfect facilities for teaching and research were created. But even more important was the task of assembling the men and brain power for operating this splendid workshop. Von Noorden selected a staff of assistants who had extensive training in clinical medicine as well as laboratory work and had proved themselves successful in research. Hugo Salomon came with von Noorden from Frankfurt and became his first assistant in Vienna, helping in the organization of the institution. Each assistant had a staff of interns, volunteers and medical students, all eager to learn, to participate in research work; the clinic swarmed with busy scientists. Every morning von Noorden gave a two-hour lecture for medical students, after which he had a conference with his assistants. Finally he made rounds in the wards. Even before the new building was opened, many problems of internal medicine and related sciences were investigated and important new facts published. The First Medical Clinic of Vienna became famous for its contributions to medical science. Doctors from all over the world flocked to this institution for postgraduate studies, among them many Americans. There were continual postgraduate courses for Americans given in English. Soon all assistants became members of the Viennese medical faculty on the basis of their research work and teaching abilities.

Von Noorden married twice. His first wife, Agnes, neé Binz, died in 1917; his second wife, Hertha, neé an der Heiden, still lives in Vienna. Three of his four children by his first marriage are living in Germany: Elisabeth Grafe, Laufenburg; Dr. med. Karl von Noorden, Baden-Baden, and Dr. jur. Hans von Noorden, Berlin. The fourth, Dr. rer. pol. Roda Wieser, lives in Vienna. Among the grandchildren, Dr. med. Gunter von Noorden works in the United States as an ophthalmologist at the University of Iowa, Iowa City.

Von Noorden was not only a great doctor and scholar, but a man of outstanding personality. The imposing demeanor of the tall man was mitigated by his friendly smile and his sympathetic way of talking. He was straightforward, sincere, unbiased, liberal in his outlook. Disinclined to ceremonial conduct, he gave his opinions in simple language, but every sentence hit the mark. He was a devoted husband and father, as well as a faithful friend, and an understanding adviser of his many patients.

His manifold activities required the utmost concentration and organization. In spite of his tremendous productivity, von Noorden found time for travel. He visited almost every country of Europe, parts of Africa, and the United States. These were professional calls for consultation, or lectures, or trips for recreation. In the United States he spoke about diabetes as the Herter lecturer

at New York University in 1905. In a second trip to the United States he was a delegate of Austria to the Twenty-third International Congress on Hygiene in Washington (1912); on this occasion he lectured in St. Louis, San Francisco, New York, Baltimore, Syracuse and Rochester. He also attended a reception of President Taft and visited Dr. Joslin in Boston.

Von Noorden was interested in many things but did not have enough leisure time to indulge in hobbies. His work in dietetics required extensive knowledge of foods, and he not only contributed to the science of dietetics but also became a connoisseur of food. He knew the particular food products and the way to prepare the dishes of the outstanding food shops and restaurants of every big city in the world. He was a gourmet of exceptional experience and a perfect cook. He was a connoisseur of fine wines too; his dinner guests were served the rarest vintages. The author once had the pleasure of having von Noordens as dinner guests. Von Noorden recognized correctly not only the provenance of the wine served, but the exact location of the vineyard and the year of vintage as well.

This is the hundredth anniversary of von Noorden's birth. After many years of work in the same field of medicine, the author admires more than ever von Noorden's genius and dedicates this biography to the memory of this great man in everlasting gratitude and friendship.

An Appreciation

Elliott P. Joslin, M.D., Boston

Until the closing years of the nineteenth century diabetes was an obscure and neglected disease. Therefore, Carl von Noorden's entry into medicine was fortunate both for doctors and diabetics. He had a dynamic personality and a wonderful gift for imparting knowledge with the written word. He popularized diabetes. He emphasized calories, the importance of which had never been adequately recognized. As a result, doctors turned to the laboratories and patients measured their diets, and both discovered that control of diabetes was worth while. Von Noorden had the art of stating the principles of diabetic metabolism in ways which doctors, previously quite unacquainted with them, could comprehend.

Von Noorden's contributions to medical literature were prodigious. It mattered little whether he wrote for students and scientists or clinical practitioners; each new volume or edition was eagerly awaited. It was with the greatest regret that a ninth edition to follow that published with Isaacs in 1927 never appeared.

By no means should one conclude that von Noorden's teaching was confined to diabetes. Following in the footsteps of Nothnagel in Vienna, he broadened and modernized the First Medical Clinic. Not the least of his gifts was his ability to pick out and develop able assistants.

I knew Professor von Noorden personally. He was an eminent man; a kind-hearted, friendly man; a doctor who intuitively saw how he could help others as individuals or as a group and took a great deal of pleasure in doing so.

BOOK REVIEWS

FOUNDATIONS OF NUTRITION. *By Clara M. Taylor, Ph.D., Grace MacLeod, Ph.D., and Mary Swartz Rose, Ph.D. $6.00, pp. 620, Macmillan Company, New York, 5th edition, 1956.*

In its present revision, this book is suitable for standard elementary college text or reference. The language is relatively simple and readable. Many of the pictures and illustrations are well selected and effective. The historical material is the same and is interesting.

Changes in the 1953 National Research Council Recommended Allowances are given. These are based on age rather than activity, yet the authors have added sufficient data on the measurement of energy for different activities.

In the chapter, "Food in Relation to Growth and Weight Control," a new short section has been added on psychological factors related to food intake. New viewpoints on the etiology of obesity are described briefly.

In all chapters where it would be pertinent, new studies or surveys are reviewed as well as the older ones, e.g., the Bataan experiment with enriched rice.

Discussion of minerals and vitamins has been revised so that related ones are grouped together. Calcium requirements of adults are brought up-to-date. The functions of fluorine in preventing dental caries and animal protein in kwashiorkor are given special attention. Some of the vitamins not now known to be nutritionally essential for humans have been omitted.

Pictures of food sources of various nutrients are confusing. The foods known are not always the best; perhaps comparison of good and poor sources is the intent but this is not apparent.

Much space is given to discussion of the "shares" method of illustrating comparative food value. Appendices give tables in both shares and weights. The latter are more practical and useful, since the share method is not generally used by nutritionists. Other reference tables use weights only.

Nothing is included on the newer knowledge of fat metabolism and essential fatty acids.

In the chapters on applications of nutrition information to individual and family problems of nutrition, much useful information is given. However, the menus suggested are often outdated and unrealistic in relation to current eating and food preparation trends.

The rapid progress of the science of nutrition during the past twelve years is incompletely developed in the revised edition of this book.

SYMPOSIUM ON NUTRITION AND BEHAVIOR, NO. 14. *Edited by Joseph Brozek, guest editor. $2.50, pp. 124, The National Vitamin Foundation, Inc., New York City, 1957.*

This symposium was held at the University of Minnesota in April, 1956. The collection of papers presents several groups of discussions. The main areas attacked are, "The Impact of Diet on Behavior"; "Hunger and Appetite"; "Food Appraisal and Acceptance by Man"; and "Satiety and Weight Control." The authors of the individual papers are recognized students of their selected topics and present the results of their own original investigations. It becomes evident that there is a real relationship between nutrition and behavior. This has been known for some time, and one of the classic examples is the dementia associated with pellagra.

What is equally important is the relationship of the nutritional factors to the so-called degenerative diseases.

Every practitioner who has a little spare time could utilize it most effectively by reading this volume.

SYMPOSIUM ON ENDOCRINES AND NUTRITION, NO. 15. *Edited by Frank H. Bethell, M.D., guest editor. $2.50, pp. 104, The National Vitamin Foundation, Inc., New York City, 1957.*

Dr. Frank H. Bethell has succeeded in bringing together a remarkable collection of papers. The topics range from "Effects of Dietary Factors on Production of Adrenal Steroid Hormones" through newer concepts of the action of insulin to the influence of endocrine glands on digestive functions.

The discussion on the newer concepts of the action of insulin is one of the most concise and clearly presented essays that has been published on the subject. Another excellent paper is "The Influence of the Endocrine Glands on Fatty Acid and Ketone Body Metabolism."

The busy physician who does not have time to keep up to date with the experimental literature will appreciate, particularly, these authoritative, up-to-date summaries of exceedingly important, if complicated, subjects.

TECHNIQUE OF FLUID BALANCE. *By Geoffrey H. Tovey, M.D. $2.50, pp. 100, Charles C Thomas, Springfield, Illinois, 1957.*

This small book is written for the man in practice. In the introduction, the author states he is emphasizing history-taking and physical findings so that the practitioner may learn to manage patients when careful laboratory examination is unavailable.

There are nine chapters dealing with the anatomy and physiology of fluids and electrolytes, the diagnosis of abnormalities, treatment and technic of administering fluids. The anatomy and physiology are covered in a manner which should be understood easily by the average reader. Amounts are given both in mEq. and in the metric system.

Chapter Five deals with the diagnosis of body fluid abnormalities. The use of the history as a diagnostic method is well covered. However, more attention could have been paid to the physical findings, e.g., of a person with extracellular fluid compartment decrease. There might have been more discussion of skin turgor, how much of a fluid deficit exists when turgor is poor, and how skin turgor may also be decreased from tissue loss. In the same chapter, on page 42, the author implies that a serum sodium concentration of less than 135 mEq./L. is most commonly due to sodium deficit. It is more likely that the hyponatremia accompanying chronic or serious illness, which responds poorly to sodium therapy, is considerably more common.

In Chapter Six, dealing with treatment, the author uses the formula method for determining the amount of sodium deficit. This formula does not always hold in all clinical conditions. He also states that he prefers lactate over bicarbonate. In his recommended therapy for the oliguric patient there might be dispute concerning the higher fluid input he recommends. Also, it might not be agreed that all patients in oliguria should be isolated and treated with penicillin.

Disorders of carbohydrate metabolism are briefly mentioned. The author comments on the depression of the serum sodium concentration brought about by release of water from the cells secondary to hyperglycemia. The therapy of ketoacidosis is commented on but no treatment schedule is given.

All in all, the book is simply written and may be easily comprehended by the man in practice. It is short and concise. It can be recommended for the physician who is not familiar with research terminology or the intricate physiology of electrolyte and water imbalances.

CARE OF THE LONG-TERM PATIENT. *By Commission on Chronic Illness, $8.50, pp. 606, Harvard University Press for The Commonwealth Fund, 1956.*

In 1950 over five million individuals were disabled to the extent of requiring long-term care. It is estimated that this number will increase by one million every ten years. The Commission on Chronic Illness was created in 1949 as an independent, voluntary organization to study this problem, and the current volume is the second in a series of four reports of their observations. These may be summarized as follows.

The care of the long-term patient requires a coordinated program, which includes the services of medical, nursing, rehabilitation, vocational and social agencies. Home care rather than institutionalization needs to be emphasized and developed. In view of the current attitudes toward long-term illness, which are inclined toward aversion and neglect, reeducation of the professional and lay public is of primary importance.

Medical care is well oriented toward short-term illness. General hospitals are organized for acute emergencies, and professional interest tends to focus on the dramatic aspects of these problems The prolonged management of chronic illness usually receives scant attention, and services to the long-term patient are often meager. To correct this attitude, medical education, both at the undergraduate and postgraduate levels,

should include programs which emphasize the care of the individual from the long-range point of view, and the prevention of extended disability which may result either from acute or chronic disease.

Rehabilitation, an unfortunate term in its connotation of action *after* definitive medical care, should be permitted to exercise its proper function of preventing disabilities as soon as the acute medical emergency has passed. If the physician will learn this, then a cooperative effort can be made to avoid the deterioration of the patient which is due largely to neglect.

Institutional care of long-term patients has been overemphasized, and the creation of more beds for their care will not solve the problem. Many of these patients can, under suitable circumstances, be cared for as well, and more economically, at home. The inescapable conclusion of this report is that the responsibility for the care of the long-term patient belongs in the whole community.

The reviewer recommends this volume to those concerned with chronic illness for its readily comprehensible presentation of facts and specific recommendations for corrective action.

THE PATHOGENESIS OF CORONARY OCCLUSION. *By A. D. Morgan, M.A., M.D., $8.50, pp. 171, Charles C. Thomas, Springfield, Illinois, 1956.*

This book is, in the opinion of the reviewer, the most significant work on the subject of arteriosclerosis since the symposium edited by Cowdry in 1933. The reason for this is that the author takes the broad viewpoint; he lifts his eyes and sees the horizons—a most desirable procedure in a field so dominated by unitarian biochemical and statistical hypotheses that Duff and McMillan were forced to remark, in a valuable recent review, that "the casual reader of recent literature might wonder whether some authors conceive of an atherosclerosis so independent of the vessel wall that it may occur in the absence of the blood vessels themselves."

Dr. Morgan takes us back to the blood vessels, first with an historical review which is remarkable for combining lucidity, brevity and inclusiveness, then with a morphological study which is balanced and, on the whole, convincing. With a refreshing lack of emphasis on cholesterol and lipoproteins, he presents and illustrates his observations and gives reasons for applying now one, now another, of the various hypotheses that have appeared in the literature. On the whole, he favors the thrombogenic theory of Duguid, interpreting coronary *occlusion* (as distinct from lesser degrees of atherosclerosis) as the result of old or recent thrombosis, and regarding the deposits of fibrin so readily demonstrable in the larger atheromatous plaques as indicating that such plaques may be the result of previous thrombosis rather than of lipid infiltration. In so doing, he gives credit to various observers, from Rokitansky on, who have contributed to this point of view. Also, he takes care, like Duguid, not to claim that all atherosclerosis may be explained as the result of thrombosis, and to admit that lipid infiltration may play a part in contributing to the formation of the smaller plaques. However, the emphasis is toward regarding lipids as secondary, aggravating factors rather than primary incitants. Indeed, as the author points out, a good case can be made out for the new trend toward examining the effect of diet on the coagulability of the blood rather than emphasizing its lipid content alone.

There are minor defects. The chapter on "Correlations" suffers, as the author admits, from a paucity of cases. The conclusion (from the London Hospital records) that coronary atheroma has not increased in the past fifty years, while coronary occlusion has, may be questioned if one realizes how inadequately atherosclerosis is quantitated at the usual autopsy table. The increase in coronary occlusion, of course, can hardly be doubted, since it is one of the pressing problems of our time.

The refreshingly broad outlook of the author is well expressed in a few sentences taken from his concluding chapter: "Thus, many a seeker after the cause of atherosclerosis has touched some facet of the truth and mistaken it for the whole. It has been variously claimed at one time or another that atherosclerosis is due exclusively to cholesterol, to haemorrhage, to thrombosis, to chylomicrons, to physiological ageing, to mucoid degeneration and to a whole series of anomalies of lipid metabolism. Some, observing one attribute, have proffered a new definition of atherosclerosis in terms of this attribute. The truth is that atherosclerosis is each and all of these things and many more, some of them no doubt still to be discovered. It is that tendency to think of 'fatty infiltration,' 'atheroma' and 'arteriosclerosis' as aetiological entities rather than makeshift descriptive terms, that leads to error and retards advances. Indeed, the evidence suggests that we may be wrong in regarding atherosclerosis as a specific disease rather than a nonspecific reaction by the artery wall to a variety of noxious stimuli. There is a limited number of ways in which an organ or a tissue may alter morphologically, and it may be that atherosclerosis is one type of reaction to a variety of insults."

PRACTICAL PEDIATRICS. *By R. Cannon Eley, M.D., and Benjamin Kramer, M.D. $7.00, pp. 309, the McGraw-Hill Book Company, Inc., New York, 1958.*

This book is one of a series for the general practitioner. The authors are all well recognized authorities in their respective fields. Of the present volume they state that their purpose ". . . is to describe in simple language accepted practices and procedures in pediatrics which can readily be acquired and practiced by the general practitioner and to present those aspects of pediatrics which are most likely to challenge the practitioner in his everyday practice." Currently accepted opinions and practices in many pediatric areas are clearly and succinctly stated. Of particular merit are the chapters on "The Newborn," "The Premature Infant," "The Management of Meningitis," "Immunization Procedures," "Fluid and Electrolyte Balance" and "Poisoning." Diabetes mellitus is discussed briefly and in broad generalities. The management of infants born of diabetic mothers is given in greater detail. Some important entities such as cretinism and pediatric endocrine problems in general are not accorded sufficient consideration; others receive more than their due.

ABSTRACTS

Aoyama, Shigeto; and Kolff, Willem J. (Cleveland Clin. Found. and Frank E. Bunts Educational Inst., Cleveland, Ohio): SEVERE DIABETIC ACIDOSIS TREATED WITH THE ARTIFICIAL KIDNEY: REPORT OF A CASE COMPLICATED WITH ACUTE RENAL FAILURE. J.A.M.A. *166*:9-11, January 1958.

A young woman in diabetic coma received 7,000 ml. of saline solution in eighteen hours but no sodium lactate or sodium bicarbonate. On the fourth day of coma the serum carbon dioxide combining power was 5.5 mEq. per liter and anuria was present. Hemodialysis for six and one-half hours resulted in a reduction of the blood urea from 117 to 48 mg. per 100 ml. Although the urine output improved, five days later the blood urea rose to 171 mg. per ml. and the patient was treated again for six hours with the artificial kidney. Following this she steadily improved and was treated in the conventional manner with diet and insulin.

Barta, L. (First Dept. Pediat., Budapest University Med. School, Budapest, Hungary): CORTISONE AND HYPOGLYCEMIC SHOCK. Lancet *1*:322-23, Feb. 8, 1958.

The author discusses the role of cortisone in combating hypoglycemic shock and suggests that it promotes rather than inhibits the uptake of glucose by the tissues.

Bayne, Stephen (Dept. Biochem., St. Salvator's Coll., St. Andrews, Scotland): ENZYME TESTS FOR GLUCOSE. Lancet *1*: 263, Feb. 1, 1958.

The author comments on the specificity of the Clinistix test for glycosuria. Mention is made of glucosone and 2-deoxyglucose, both of which react with Clinistix and Tes-Tape, but which never have been reported in urine. The latter sugars are, however, being used increasingly in metabolic studies.

Bertram, F.; Bendfeldt, E.; and Otto, H. (Second Medical Clinic, General Hospital, Hamburg-Barmbek, Germany): CURRENT STATUS OF THE ORAL DIABETES THERAPY: CLINICAL EXPERIENCE WITH BZ-55 AND D-860. Schweiz. med. Wchnschr. *87*:25-30, Jan. 12, 1957.

BZ-55 (carbutamide) frequently has a more intensive "antidiabetic" action. D-860 (tolbutamide) can be used in slightly higher dosage to compensate for its minor activity. The indications for both preparations are the same. Both are without effect in diabetes caused by lack of insulin while the type of diabetes that is still producing insulin—what Bertram calls "counter-regulation-diabetes"—is responsive. Responsiveness depends on age, type of constitution, duration of the preceding insulin therapy and partly also on the previous insulin dose. The duration of the diabetes is unimportant. BZ-55 is a sulfonamide and reduces—in some cases only temporarily—colon bacilli in the intestine. Apparently this is clinically without significance. Both drugs give rise to allergic skin reactions, which are rarer with D-860 and more frequent with BZ-55. In most instances of skin allergy it is possible to replace one preparation by the other. Crossed allergy is rare. Subjectively both drugs are evenly well tolerated. (German)

Bicknell, Franklin (London, W. 1, England): EFFECT OF CERTAIN PROTEIN FOODS ON BLOOD-SUGAR LEVELS AND GLUCOSE TOLERANCE. Lancet *2*:388, Aug. 24, 1957.

Conclusion of this study: Patients taking soluble insulin before dinner in the evening are less likely to have hypoglycemia if they eat hot meat than if they eat the same amount of cold meat.

Boucot, Katharine R. (Woman's Med. Coll. of Pennsylvania and Philadelphia Dept. of Health, Philadelphia, Pa.): DIABETES MELLITUS AND PULMONARY TUBERCULOSIS. J. Chron. Dis. *6*:256-79, September 1957.

Diabetics are more susceptible to tuberculosis than are nondiabetics. Patients with tuberculosis have no enhanced susceptibility to diabetes. While tuberculosis mortality rates have dropped markedly, the rate of newly reported cases of active tuberculosis has not fallen proportionately. While this may be due to improved case-finding efforts, it also may be a reflection of better therapy, which allows the tuberculosis patient to live long enough to die of a nontuberculous disease. "Diabetic tuberculosis" is a fulminating disease. Early detection is of special importance in this era when potent antimicrobial drugs are available that exert their maximal effectiveness precisely on the type of acute exudative tuberculosis characteristically found in diabetics. Once cavitation has taken place, treatment is much more difficult. Suitable case-finding programs for diabetics include tuberculin testing at the time of diagnosis of diabetes and, for nonreactors, annually thereafter. Reactors to tuberculin should receive thorough clinical and radiologic study, including at least semi-annual chest X rays. The source for infection should be carefully sought in order to be sure that susceptible diabetics are not living in intimate contact with open cases of tuberculosis. Causes for the diabetic's increased susceptibility to tuberculosis are not known, but various combinations of factors involved may be biochemical, hormonal, immunologic, nutritional, or hereditary.

Burt, Richard L.; and Julian, Nancy (Dept. Obstet. & Gynec., Bowman Gray Sch. of Medicine of Wake Forest Coll., and North Carolina Baptist Hosp., Winston-Salem, N. C.): THE UTILIZATION OF FRUCTOSE IN NORMAL PREGNANCY AND IN PRE-ECLAMPSIA. Obst. & Gynec. *11*:372-78, April 1958.

Detectable intolerance to fructose develops in pre-eclampsia. The defect in utilization is not as striking as that of glucose, possibly because of alternative pathways for fructose metabolism. Unknown factors, other than insulin resistance developing in pre-eclampsia, are believed to be responsible for the changes observed.

Caillouette, James C.; and Russell, Keith P. (Dept. of Obstetrics and Gynecology of Los Angeles County Hosp., and University of Southern California Sch. of Med., Los Angeles, Calif.): FACTORS RELATED TO STILLBIRTHS: AN ANALYSIS AT THE LOS ANGELES COUNTY HOSPITAL. Obst. & Gynec. *11*:164-69, February 1958.

A review article of factors related to stillbirth that includes five cases of diabetes mellitus. The authors concluded that infants of mothers with diabetes ideally should be delivered at thirty-four to thirty-six weeks' gestation.

Carrington, Elsie R.; Reardon, Helen S.; and Shuman, Charles R. (Temple University School of Medicine and Hosp. and St. Christopher's Hosp. for Children, Philadelphia, Pa.): RECOGNITION AND MANAGEMENT OF PROBLEMS ASSOCIATED WITH PREDIABETES DURING PREGNANCY. J.A.M.A. *166*:245-49, Jan. 18, 1958.

A metabolic disorder must be suspected in patients whose records include any of the following features: a family history of diabetes, obesity, glycosuria during pregnancy, previous stillbirth or neonatal loss, repeated abortion, oversized infants and hydramnios. Prediabetics can be diagnosed with certainty only by means of the glucose-tolerance test. The condition of 790 patients whose pregnancy record revealed one or more of the above clinical features was studied by the conventional three-hour oral glucose-tolerance test. In 111 of the patients (14 per cent) the fasting blood sugar was less than 120 mg. per 100 cc. and the two-hour levels exceeded 120 mg. per 100 cc. They were classified as prediabetics. The previous fetal loss in this group was 30 per cent. This corresponded to the 25.6 per cent fetal mortality rate in thirty-nine untreated cases unregistered or unrecognized before delivery. On the other hand the fetal loss in seventy-two treated cases during recent pregnancy was 2.9 per cent. Early recognition of prediabetes in the gravid woman and careful metabolic and obstetric management should result in delivery of a normal baby. These measures and meticulous care of the infant during the critical neonatal period are essential to the successful outcome of pregnancy in the prediabetic state.

Clinicopathological Conference (University of Kansas Medical Center, Kansas City, Kansas): DIABETES MELLITUS, HYPERLIPEMIA AND RECURRENT ACUTE PANCREATITIS. CASE PRESENTATION. J. Kansas M. Soc. *58*:756-63, November 1957.

The patient was a known diabetic who came in with acute, severe abdominal pain suggesting a ruptured viscus. The initial absence of physical signs of peritonitis suggested acute visceral injury; the later appearance of peritoneal irritation pointed to acute pancreatitis. This was clearly the primary feature of the terminal illness. Diabetic acidosis must have been of secondary importance.

Deuil, Roger (French Diabetic Association, Paris, France): TREATMENT OF DIABETES WITH HYPOGLYCEMIANT SULFONAMIDES. Med. Digest *25*:1-9, January 1957.

Even though attractive, this treatment cannot be recommended unconditionally. The author warns that a period of observation will be required to determine the extent and limits of this type of treatment.

Duncan, Garfield G. (Philadelphia, Pa.): INSULIN THERAPY FOR DIABETES. Maryland M. J. *6*:54-58, February 1957.

About 80 per cent of diabetic patients are overweight when they first consult their physician for treatment. Insulin can be avoided in these cases by utilizing a reducing program. Nearly every thin adult diabetic will give a history of having been overweight at one time. Most papers pertaining to diabetes deal with the subject of insulin therapy. Not enough attention is given to the 80 per cent of patients whose diabetes could be controlled without insulin when they first seek treatment. The child diabetic and the thin diabetic are the ones to whom insulin should be given from the outset of therapy. A fairly small percentage of patients needing insulin do very well with one dose of an intermediate-acting insulin, given three-quarters of an hour or an hour before breakfast.

The second plan for diabetes of slightly greater severity is a mixture of NPH insulin and regular (unmodified, soluble or crystalline) insulin given a few minutes before breakfast each morning. A considerably larger group of patients is controlled with this program. The third program, for the most severe diabetes, is a mixture of NPH insulin and regular insulin before breakfast with a small dose of NPH insulin after supper.

Diabetes is well controlled in patients who follow prescribed diets. There is also a much smaller group who follow their own diet. From this second group come over 70 per cent of readmissions to the hospital. The three plans of insulin therapy are satisfactory but may be further simplified. For that group with severe diabetes, who receive NPH and regular insulin before breakfast and a dose of NPH insulin after supper, the physician may wish to eliminate the evening dose. When the diabetes is controlled on this program, it is possible to try a two–to–one mixture—two of regular insulin to one of Protamine Zinc insulin. That is the only place Protamine Zinc insulin has in the treatment of diabetes as of now.

Duncan, Garfield G. (Philadelphia, Pa.): PRESENT STATUS OF ORAL THERAPY FOR DIABETES. Pennsylvania M. J. *61*:46-48, January 1958.

The author's experience with somewhat more than 130 patients who were given tolbutamide, and a review of the experience of others, indicate the following: All diabetic patients who acquired diabetes after forty years of age, who are not appreciably overweight, who have no acute complications, and who require insulin to control the diabetes are candidates for a trial therapy with tolbutamide. For those who are overweight, tolbutamide therapy may be given advantageously, but this should be considered a temporary measure, and one to be discontinued when a suitable reduction in weight achieves control of the diabetes without it. Substitution of tolbutamide therapy for correction of obesity will probably be widespread. This practice is to be deprecated. Fortunately, tolbutamide does not stimulate the appetite. This is one advantage that it has over insulin therapy in treating patients who are overweight. In considering tolbutamide therapy, it is a good plan to be sure that the patient needs drug therapy before embarking on a treatment that may not be necessary. Insulin may be withdrawn abruptly when the requirement does not exceed 20 units daily. If glycosuria in increasing amounts occurs, a trial of tolbutamide therapy is justified. Prompt control of the glycosuria will be proof of its effectiveness. If the insulin dosage exceeds 20 units, the amount given may be reduced by one half for the first day and omitted on the second day if no glycosuria occurs. The prompt appearance and increase of ketonuria during the first twelve hours indicates that no benefit need be expected from tolbutamide and that insulin therapy should be promptly resumed if unfavorable progression of the ketosis is to be avoided. If tolbutamide is given only to patients who must take insulin without it, a considerable percentage are obliged to return to insulin therapy within four to ten months without any apparent cause. This experience will be largely obscured if tolbutamide is prescribed for patients whose diabetes could be controlled by diet therapy alone.

Dyfverman, A.; and Broman, L. (Inst. of Biochemistry and the Psychiatric Clin., Univ. of Uppsala, Sweden): PAPER CHROMATOGRAPHY OF PHOSPHORIC ESTERS FROM ERYTHROCYTES OF MENTAL PATIENTS DURING INSULIN COMA TREATMENT. Scandinav. J. Clin. & Lab. Invest. 9:356-64, 1957.

Phosphoric acid esters from erythrocytes of seven mental patients treated with insulin, of two chronically schizophrenic patients who did not receive insulin, and two healthy blood donors were separated and compared visually in one-dimensional chromatograms developed with an acid and an alkaline solvent. An indication was found that insulin treatment may cause one or more substances (not yet identified) to appear, and that this substance was not influenced by single doses of the hormone. No differences were found between the chromatographic patterns of normal and schizophrenic subjects.

Editorial (Southern Med. Association, Birmingham, Ala.): HYPERGLYCEMIA IN DIABETES—IS IT DESIRABLE? South. M.J. 51:247-48, February 1958.

In 1931, Stolte advocated an undisciplined method of handling diabetics—namely avoidance of symptomatic acidosis, with no other regard to the status of the urinalysis. Opposed to this are most of the schools of thought that have been concerned for years with the management of large numbers of diabetic patients and, perhaps even more important, with the teaching of thousands of medical students and doctors. In Lowenstein's report on the method of treatment that ignores both hyperglycemia and glycosuria, the statement that, "this school (of thought) has not written a single textbook, but it has commanded the allegiances of many a practicing physician," is indeed an interesting and telling confession. He suggests another original hypothesis: that arteriosclerosis is caused by a deficiency in the quality and/or quantity of protein in the available metabolic mixture and that this deficiency is exaggerated in diabetes mellitus because of "excessive protein wastage." The fact that poorly controlled diabetics have negative nitrogen balance is an eloquent argument against the free diet regimen. The styling of hyperglycemia as "the diabetic's best friend" is certainly at variance with the exhaustion of the secretory activity of the islet cells demonstrated by Lukens and his associates.

Editorial: HYPOGLYCAEMIA AND THE MIND. Brit. M.J. 1:150-51, Jan. 18, 1958.

The author reviews hypoglycemia with regard to its etiology, presenting symptoms and signs, and medical-legal complications which may result from abnormal behavior of a patient during an hypoglycemic episode.

Ellenberg, Max (Dept. of Med., Mount Sinai Hosp., New York, N. Y.): DIABETIC NEUROPATHY: PITFALLS IN DIAGNOSIS. A.M.A. Arch. Int. Med. 100:906-15, December 1957.

Case histories are presented indicating pitfalls in the diagnosis of diabetic neuropathy. In view of the absence of any pathognomonic clinical or laboratory findings of diabetic neuropathy, the diagnosis must be based on the exclusion of all other possible explanations. It may be corroborated by the presence of increased spinal fluid total protein and by the clinical course, the author concludes.

Elrick, Harold; Witten, Thomas A.; and Arai, Yoshiaki (University of Colorado Sch. of Med., Veterans Administration Hospital, Denver, Colo.): GLUCAGON TREATMENT OF INSULIN REACTIONS. New England J. Med. 258:476-80, March 6, 1958.

Studies of the treatment of forty-one induced and spontaneous insulin reactions in eighteen diabetic patients with crystalline glucagon are presented. One or 2 mg. of glucagon administered intramuscularly or subcutaneously was found to be an effective and convenient agent for the relief of hypoglycemic attacks. The advantages of glucagon over glucose in the treatment of certain types of insulin reactions are pointed out.

Fabrykant, Maximilian (Dept. of Med., New York Univ. Post-Graduate Sch., and the Med. Serv. of Univ. Hosp., New York, N. Y.): FAVORABLE EFFECTS OF SUPPLEMENTAL ORINASE IN INSULIN-TREATED LABILE DIABETES. Metabolism 6:509-17, November 1957.

The long-term employment of Orinase as a supplement to insulin therapy was studied in six patients who were given their usual dose of insulin either from the start of Orinase therapy or after the correction of the ketosis that had been brought about by reduction in insulin dosage. The most prominent effect of such therapy was a stabilization of the diabetic condition, which allowed a gradual reduction of insulin dosage by 27 to 40 per cent of the patient's usual dose. Because of the observed beneficial effects of continuous supplemental therapy with Orinase in labile diabetes, it is suggested that such treatment be tried in all insulin-dependent diabetic patients who cannot be satisfactorily controlled with insulin alone. Experience gained in the present series indicates that the long-term administration of Orinase as an adjunct to insulin therapy may be safely initiated on an ambulatory basis.

Fagerberg, Sven-Erik (Med. Dept., Sahlgren's Hosp., University of Gothenburg, Sweden): STUDIES ON THE PATHOGENESIS OF DIABETIC NEUROPATHY. IV. ANGIOPATHIA DIABETICA VASAE NERVORUM. Acta med. scandinav. 159:59-62, Oct. 30, 1957.

Biopsies were performed on the sural nerve of about 150 patients. Diabetics in different age groups with cases of varying duration and control were represented. The preparations were first studied in order to find out whether there was any neuropathy; then they were sectioned serially and stained according to the McManus-Hotchkiss method, the so-called PAS staining. This stains the glycoproteins, which may be present in the vascular walls and which are assumed to be the pathological substrate of the diabetic angiopathy. The diabetic preparations were compared with those from control patients of about the same age. If the continued investigation shows the same tendency, the author is ready to believe that these results point to angiopathy being an important, perhaps even the only, factor in the pathogenesis of diabetic neuropathy.

Flink, Edmund B.; and Olwin, Thomas K. (Med. Serv., and Dept. of Medicine, Veterans Administration Hosp., Minneapolis, Minn.): THE TREATMENT OF DIABETIC ACIDOSIS. Lancet 78:37-42, February 1958.

A form of therapy for diabetic acidosis is presented which is based on knowledge of deficits that occur during the development phase of acidosis. Major emphasis has been placed on a correct diagnosis, large doses of insulin given early, treatment of allied and precipitating conditions, early and repeated determinations of glucose and ketone levels, and a reasonable approach to replacement of fluid and electrolyte deficits known to exist in diabetic acidosis.

Franklin, Edward C., and Weissman, Milton (Dept. of Med., and Lab. Serv., Veterans Admin. Hosp., Bronx, N. Y.): SERUM LIPIDS IN LIPEMIA RETINALIS: REPORT OF A CASE. Ann. Int. Med. *46*:413-19, February 1957.

Lipemia retinalis is nearly always associated with diabetes complicated by acidosis. The serum from these patients is grossly milky and is associated with hyperlipemia. Serum lipid studies in the case reported revealed initially high serum levels of total fat, cholesterol, phospholipids and neutral fat; the patient also had many xanthomata. With treatment of the diabetes, the serum hyperlipemia cleared, and two months later the xanthomata of the skin had entirely disappeared.

Frazer, Samuel C. (Dept. Clinical Chemistry, Royal Infirmary, Edinburgh, Scotland): ENZYME TESTS FOR GLUCOSE. Lancet *1*:166, Jan. 18, 1958.

The author reports his experience with enzyme tests for glycosuria. False positive reactions may be obtained when either hydrogen peroxide or hypochlorites are present in the urine. The first is largely of theoretical interest but many household and laboratory cleansers contain hypochlorites and false positive reactions can arise from gross contamination of urine containers. The author states that he is unaware of a false positive enzyme test for glycosuria in an uncontaminated urine specimen where glucose was proved to be absent by special tests, such as paper chromatography.

Froesch, E. R.; Prader, A.; Labhart, A.; Stuber, H. W.; and Wolf, H. P. (Pediat. Clin., Med. Policlin., Inst. for Physiological Chemistry of the University of Zurich, Switzerland): THE HEREDITARY FRUCTOSE INTOLERANCE, A SO FAR UNKNOWN CONGENITAL ERROR OF METABOLISM. Schweiz. med. Wchnschr. *87*:1168-71, Sept. 14, 1957.

An as-yet-unknown inborn error of fructose metabolism is reported. The disorder differs from the so-called essential fructosuria by the occurrence of hypoglycemia and severe symptoms upon ingestion of fructose. The mode of inheritance is probably of the autosomal recessive type. The disorder was found in four patients, all related. In these patients the administration of fructose lead to its excessive and prolonged concentration in blood and to the excretion in urine of approximately 10 per cent of the ingested fructose. Concurrently with the rise in blood fructose, blood glucose fell to as low as 10 mg. per cent. This severe hypoglycemia lasted for as long as several hours and was accompanied by nausea, hemorrhagic vomiting, trembling, profuse sweating and somnolence. After cessation of acute symptoms, slight and transient hyperbilirubinemia and albuminuria were observed. An allergy to fructose was excluded as a cause of this disorder. It may have been due to the congenital absence of an enzyme responsible for one of the steps of fructose metabolism by the fructose-1-phosphate-triose pathway. Possible mechanisms for the development of the hypoglycemia and toxic symptoms are discussed. (German)

Furnivall, Mary (St. Bartholomew's Hosp., London, E.C. 1, England): LABORATORY DIAGNOSIS OF CONGENITAL GALACTOSAEMIA AT BIRTH. Lancet *1*:163, Jan. 18, 1958.

The author suggests that one of the commercial milk powders available in her country, marketed under the name of Farex (Galaxo) contains 5 per cent separated milk powder and 2.5 per cent lactose. In view of the varying tolerance to lactose of infants with galactosemia, it seems advisable that those who use Farex should be aware of its composition.

Grodsky, G. M. (Dept. Biochem., Univ. of Cambridge, England): AN ASSAY OF INSULIN BY FIBRIL FORMATION FROM SMALL SAMPLES OF PANCREAS. Biochem. J. *68*:142-45, January 1958.

The author describes the chemical method for the assay of insulin in 1 gm. samples of pancreas tissue, utilizing the phenomenon of fibril formation. Recoveries are linear and near quantitative. The levels of insulin found in ox, pig, sheep, calf, cat and rat pancreas were comparable to those attained by bio-assay. An apparatus is described for simultaneous determination of eighteen samples.

Grunberg, A.; and Blair, J. L. (Diabetic Centre, St. Catherine's Hosp., Birkenhead, England): HYPOPITUITARISM WITH CONSECUTIVE DEVELOPMENT OF DIABETES MELLITUS. Brit. M. J. *2*:439-41, Aug. 24, 1957.

A case of hypopituitarism is reported in which diabetes mellitus developed after at least twenty years of deficient pituitary function. The clinical findings and laboratory investigations are described, with special reference to the behavior of the diabetic state under the influence of various hormones.

Gumpel, Roy C.; Vongries, Alexander G.; and Ralli, Elaine P. (Lenox Hill Hosp.; New York University-Bellevue Med. Center, New York, N.Y.): TOLBUTAMIDE (ORINASE) IN THE TREATMENT OF THE AMBULATORY PATIENT WITH DIABETES MELLITUS. J. Am. M. Women's A. *13*:39-45, February 1958.

The effects of tolbutamide (Orinase) were studied in sixty-nine patients with diabetes mellitus. Forty-four were successfully treated with tolbutamide and have now been observed for periods of from four to twenty-one months. Of the successfully treated group, twelve had not required insulin, except for two patients who had received insulin intermittently, prior to tolbutamide therapy. However, the blood sugar levels in these patients were well above the normal limits and were associated with considerable glycosuria. The other thirty-two patients had all required insulin and had been receiving insulin for from one month to seventeen years. The pertinent fact about the patients who did not respond to tolbutamide therapy was the duration of the diabetes. Half of the patients in this group had required more than 30 units of insulin daily to control the diabetes. No serious side effects from the drug were noted. Although a rash occurred in seven patients, none showed any abnormality in the number or character of the white blood cells. Tolbutamide appears to provide a method of therapy that is useful in the older diabetic patient.

Haarstad, Jens (Med. Dept., Diakonhjemmets sykehus, Oslo, Norway): HORMONE-PRODUCING INSULOMA IN DIABETES MELLITUS. Acta med. scandinav. *159*:247-49, Nov. 29, 1957.

The author describes the case of a patient with diabetes mellitus complicated by the occurrence of a hormone-producing insuloma. Clinical data and autopsy findings are reported. Three previously published cases are mentioned.

Hay, K. M. (Birmingham, England): HYPOGLYCAEMIA AND THE MIND. Brit. Med. J. *1*:341, Feb. 8, 1958.

The author comments on his observation that functional hypoglycemia is commoner than suspected. He feels that the prevalent habit of going to work without breakfast is the cause of many of the attacks.

Jahnke, K. (Med. Clin. and Polyclin. of the Med. Academy of Düsseldorf, Düsseldorf, Germany): CLINICAL EXPERIENCES

WITH A NEW ORAL TREATMENT OF DIABETES MELLITUS. Med. Digest 25:11-16, January 1957.

A cure of the diabetes mellitus by the new substances is not possible. In light cases, one can see a long-standing remission of the diabetes, after which further use of the medicine is superfluous. Later on it may be necessary again.

Jaumann, R. (Med. Policlin., Zürich, Switzerland): THE ROLE OF THE SUPRARENAL CORTEX IN ANTAGONISM TO INSULIN IN DIABETES MELLITUS. Schweiz. med. Wchnschr. 87:1069-72, Aug. 17, 1957.

Intravenous insulin tolerance tests were carried out in eight diabetics and plasma 17-21-hydroxycorticoids estimated before, one hour and four hours after the administration of insulin. No distinct difference could be detected between stable and brittle diabetics with regard to the blood sugar response and the behavior of the plasma 17-21-hydroxycorticoids. The fasting plasma 17-21-hydroxycorticoid levels were all within normal limits. It has been demonstrated that, in the diabetic, a sudden fall of blood glucose due to insulin may lead to a stimulation of the adrenal cortex even though hypoglycemia was not profound enough to cause any symptoms. There was no indication pointing to an increased adrenal cortical activity in diabetes. (German)

Jensen, S. Eskjær; Lundbaek, K.; Møller, Bent; and Rafaelsen, O. J. (Second University Clin. of Internal Med., Kommunehospitalet, Aarhus, Denmark): EFFECT OF ORAL ANTIDIABETIC DRUGS ON BLOOD-SUGAR AND INORGANIC PHOSPHATE CURVES IN ORAL AND INTRAVENOUS GLUCOSE TOLERANCE TESTS. Acta med. scandinav. 160:67-74, Jan. 31, 1958.

After administration of the oral antidiabetic drugs carbutamide or tolbutamide for thirty-six to sixty hours, patients with diabetes mellitus revealed an improvement in glucose-tolerance in both oral and intravenous tolerance tests. However, during this improvement no change in the serum inorganic phosphate curve occurred. These results argue against the assumption that the effect of oral antidiabetic drugs is due to a stimulation of the insulin production or to an inhibition of an insulinase.

Johnson, Doris (Director, Dept. of Dietetics, Grace-New Haven Community Hosp., New Haven, Conn.): PLANNING A RESTRICTED SODIUM DIET AND BLAND, LOW-FIBER DIET FOR THE DIABETIC PATIENT. Am. J. Clin. Nutrition 5:569-74, September-October 1957.

The author outlines modifications of the exchange lists of diabetic diets so that a bland, low-fiber and restricted sodium diet can be obtained. The change to this type of diet does restrict and limit the patient's selection of foods quite markedly. Sample meal plans are outlined in the article.

Joiner, C. L.; and Lee, C. T., Jr. (Guy's Hosp., London, England; and The Pennsylvania Hosp., Philadelphia, Pa.): CLINICAL TRIAL OF CARBUTAMIDE (BZ-55) IN DIABETIC OUTPATIENTS. Guy's Hosp. Rep. 106:288-99, 1957.

Forty-nine diabetic patients with diabetes of varying grades of severity were given carbutamide in an outpatient trial of the drug. The comparison of glycosuria and fasting blood sugar values between separate two-week periods of placebo and carbutamide administration was used to determine the degree of response to the drug. Following the controlled trial, forty-seven of the forty-nine patients were continued on carbutamide for between one and six months and the results observed. Despite the fact that 80 per cent of the patients showed some degree of improvement in control, it was felt that in only eight patients, or 18 per cent of the total group, was the drug really indicated, and then only if it should prove nontoxic on prolonged administration. No instances of severe hypoglycemic reactions or of diabetic ketosis were seen in the group of patients using the methods described here to determine responsiveness to carbutamide.

Kaartinen, Matti; Hall, Mauri; and Osterman, E.: WAKING THE INSULIN-COMA PATIENT WITH GLUCAGON. Duodecim 73: 530-39, 1957.

After a short historical and theoretical review, the authors report upon twenty-three patients waked from deep psychiatric insulin coma with the new pancreatic hormone preparation Glucagon 1%. It was given in thirteen cases intravenously and all patients woke (therefore could drink) within nine to fourteen minutes. The intramuscular route was used in ten cases; one patient only had to be waked with glucose intravenously after twenty minutes; all others woke within sixteen to twenty-two minutes. The insulin doses used were 80-400 IU. The glucagon dose was 0.02-0.1 mg./kg. body weight. The method used seems to be simple and safe. It is better than the old method of waking with glucose solution transnasally. (Finnish)

Keup, W. (Psychiatric Hosp., Marsens/Fribourg, Switzerland): INSULIN THERAPY OF PSYCHOSES WITH AMORPHOUS INSULIN AND HYALURONIDASE. Schweiz. med. Wchnschr. 87:1128-31, Aug. 31, 1957.

During insulin shock therapy of ten schizophrenic patients, crystalline insulin was employed at the outset and was successively replaced by "Insulin Novo Amorph" and by amorphous insulin injected intramuscularly with hyaluronidase. The saving of insulin through this procedure averaged 56.5 per cent, or 128 units. With the combination described above, the dosage for coma therapy lay between 50 and 160 units of insulin. Unfavorable effects were not observed. Favorable effects observed were: a shorter period up to the onset of coma, sometimes with a shortened pre-coma; a smoother and calmer course of therapy; a more rapid awakening after administration of sugar; greater calm among the patients, and diminished danger of after-shock. The patients receiving hyaluronidase showed a smaller depression of the blood sugar in spite of a deep coma. The mechanism of the action produced by this method, and its economic aspects, are discussed briefly. (German)

Kleeberg, J. (Haifa, Israel): BLOOD-SUGAR ESTIMATION. Brit. M. J. 2:1305, Nov. 30, 1957.

The author describes a caramelization test for blood sugar estimation which may be executed with glassware and chemicals from a G.P.'s small routine laboratory. This test is based on Moore's reaction, according to which glucose and other hexoses are caramelized by heating in a strongly alkaline solution to a brownish yellow product, the intensity of color varying with the concentration of glucose in a given liquid. The resulting shades of yellow permit a rough estimation of the glucose level with an accuracy of about 50 mg. per cent.

Klein, R.; Marks, J.; and Mirsky, I. A. (Children's Hosp., Pittsburgh, Pa.): INSULIN-PRODUCING CAPACITY OF THE PANCREAS IN CHILDREN WITH DIABETES MELLITUS. Quart. Rev. Pediat. 12:210, November 1957.

The relatively small amounts of exogenous insulin required early in the course of diabetes mellitus in children and the marked decrease in such insulin requirements that may follow the initial period of treatment suggest that the pancreas is still capable of producing insulin at the onset of the clinical disorder. Subsequently, however, pancreatic exhaustion and an irreversible insulin insufficiency ensue. In all children in whom diabetes mellitus was newly discovered, the hypoglycemic response to tolbutamide and indoleacetic acid was significant. Diminution and disappearance of the response occurred with increased duration of the syndrome. These studies indicate that at the onset of the diabetic syndrome, the pancreas of the child is still capable of producing insulin (relative insulin insufficiency), but subsequently this capacity is lost.

Knox, Lawrence J.; Harrison, Charles W.; and Doenges, John P. (Dept. of Med., The Olney Sanitarium Clin., Olney, Ill.): THE USE OF AN ORAL HYPOGLYCEMIC AGENT AS AN ADJUVANT IN THE TREATMENT OF DIABETES MELLITUS. Illinois M. J. *112*:201-05, November 1957.

The oral hypoglycemic agent Orinase was used with reasonable success in outpatient care of thirty-five out of forty cases of diabetes. Failures were experienced in severe and juvenile diabetics. In over one half of the cases, a rise in serum cholesterol was noted. The significance of this finding needs further study, the authors concluded.

Kohn, J. (London, S.W. 15, England): BLOOD-SUGAR ESTIMATION. Brit. M. J. *2*:1435, Dec. 14, 1957.

The author replies to a letter concerning a previously published article which described the use of Clinistix in blood sugar estimations. He substantiates the claims made in his previous article with regard to the efficiency and validity of the method he described.

Krall, Leo P. (Joslin Clinic and New England Deaconess Hosp., Boston, Mass.): THE ORAL INSULIN SUBSTITUTES. M. Arts & Sc. *11*:102-08, Third Quarter 1957.

The present status of the known, clinically tested oral hypoglycemic agents is discussed. None of these is insulin. All need a much longer period of time to demonstrate their long-range effectiveness in diabetic therapy and to demonstrate any possible toxic effects. They cannot be compared with insulin at this time. All the oral hypoglycemic agents are being extensively studied and may some day be a valuable adjunct in the treatment of diabetes. Tolbutamide is now available on prescription in the United States and Canada. Carbutamide is still being used abroad. The formamidinyliminourea group, still in the earlier phases of investigation, shows much potential. All of these substances are refocusing the thought and experimental work that may throw light on the basic causes and mechanisms of diabetes mellitus.

Kronenberg, Bernard (New York City): CURRENT STATUS OF THE THERAPY OF DIABETIC RETINOPATHY. New York J. Med. *57*:2677-80, Aug. 15, 1957.

The earliest changes visible in diabetes are venous stasis and the appearance of capillary micro-aneurysms in and around the macula. Small hemorrhages may be present as well, but many of the micro-aneurysms are thought to be hemorrhages because it is ophthalmoscopically difficult to differentiate them. It is now apparent that diabetic retinopathy is not a result of atherosclerosis but is a distinct form of vascular change. It is related specifically to diabetes and is close to the lesions described by Kimmelstiel and Wilson. Diabetic retinopathy is aggravated by pregnancy, infection, and the administration of ACTH. All three are associated with increased activity of the adrenal cortex. Patients with diabetic retinopathy also may show an increased excretion of oxysteroids indicative of an excess secretion of the adrenal cortex. Diabetic patients without retinopathy do not show this increased excretion. Another interesting claim is that diabetics with retinopathy excrete more vitamin B_{12} than those without retinopathy. When this is related to the fact that animals treated experimentally with cortisone also excrete vitamin B_{12}, the possibility of a correlation becomes apparent. Testosterone propionate depresses the adrenal cortex by inhibiting production of ACTH in the pituitary. Administration of testosterone to patients with diabetic retinopathy reduced urinary excretion of vitamin B_{12}.

Possibly because we have nothing better to offer our patients, many authors in the American and European literature agree that the rigid control of the blood chemistry of the diabetic by means of diet and insulin will prevent the onset of retinopathy. Nevertheless, despite all controls many patients do develop diabetic retinopathy, and to date we have no effective therapy.

Lapenna, Martheriga Silvestri (Rome, Italy): THE NEW ORAL THERAPY OF DIABETES MELLITUS. Med. Digest *25*:19, January 1957.

Stress has to be laid on the fact that these compounds can in no way be considered as "substitutes for insulin," the author says. Their mode of working is not yet clearly understood, but there is evidence that they act somehow on endogenous insulin, rendering it more efficient or protecting it against destruction by insulinase or other enzymatic factors.

Lapresle, Cl.; and Grabar, P. (Service de Chimie Microbienne, Institut Pasteur, Paris, France): EVIDENCE OF AN ANTIGENIC IMPURITY IN INSULIN PREPARATIONS AND A CORRESPONDING ANTIBODY IN THE SERUM OF DIABETICS TREATED WITH INSULIN. Rev. franç. études clin. et biol. *2*:1025-37, December 1957.

Certain insulin preparations contain an impurity antigenic to man. This antigen can easily be detected during redissolving before crystallization of the insulin. In respect of ox, pig and horse, the antigen is not specific for the animal from which it is derived. The antigen is not dialysable, is precipitated by trichloracetic acid and has electrophoretic mobility considerably less than insulin and different from glucagon. The human antibodies to this antigen are different from those causing allergic reactions or insulin resistance.

Lorenzen, Robert F. (Phoenix, Ariz.): VASCULAR CHANGES IN THE OCULAR FUNDUS. Arizona Med. *15*:1-6, January 1958.

Retinal changes in arteriolar sclerosis, hypertension, diabetes, and vascular occlusions are described and illustrated with fundus photographs. The author hopes this review will prove helpful to those in all branches of medicine who must interpret changes seen with the ophthalmoscope.

Lurie, Arthur S. (Boston City Hosp., Boston, Mass.): XANTHOMA DIABETICORUM. U. S. Armed Forces M. J. *9*:268-72, February 1958.

The author presents a case of xanthoma diabeticorum, an uncommon manifestation of diabetes mellitus which is the result of the hyperlipemia and hypercholesterolemia that may be associated with the metabolic disease. Treatment and management are discussed.

Maier, C. (District Hosp., Männedorf, Zürich, Switzerland): MEGALOBLASTIC VITAMIN B_6 DEFICIENCY ANEMIA WITH HEMOCHROMATOSIS. Schweiz. med. Wchnschr. *87*:1234-35, Oct. 2, 1957.

Report of a sixty-seven-year-old woman with hyperchromic megaloblastic anemia, hemosiderosis of the liver and mild diabetes. The anemia proved resistant to liver extract, vitamin B_6 and folic acid. Pyridoxin injections, 200 mg. intramuscularly daily, produced a rise of the reticulocytes with definite remission of the anemia. In the absence of a history of malnutrition, a disturbance of the intermediary pyridoxin metabolism is suspected. (German)

Marble, Alexander; and Camerini-Davalos, Rafael (New England Deaconess Hosp., and Joslin Clin., Boston, Mass.): CLINICAL EXPERIENCE WITH SULFONYLUREA COMPOUNDS IN PATIENTS WITH DIABETES MELLITUS. Med. Digest *25*:17-18, January 1957.

The mode of action of the sulfonylurea compounds has continued to be a matter of lively interest. Whatever the answer may be it seems apparent that one must proceed cautiously in the use of the sulfonylurea compounds. One needs to know by careful studies over months and years of time the effect of the drugs on various organs and their functions—in particular, any deleterious effects on liver function. Until such information is available, the use of these compounds should be regarded as an investigational trial and not as definitive treatment.

Marks, Leon J.; Weiss, Daniel M.; Leftin, Jehaudah H.; and Rossmeisl, Elsie C. (Psychiatry and Neurol. Serv. and the Steroid Res. Lab., Veterans Administration Hosp., Boston, Mass.): THE ADRENOCORTICAL RESPONSE TO INSULIN COMA. I. EFFECTS OF AN ENTIRE COURSE OF INSULIN COMA THERAPY ON THE URINARY EXCRETION OF 17-HYDROXYCORTICOSTEROIDS AND 17-KETOSTEROIDS AND ON CIRCULATING EOSINOPHILS. J. Clin. Endocrinol. *18*:235-45, March 1958.

Adrenocortical function was measured before, during and after a complete course of insulin coma therapy in a paranoid schizophrenic patient. During the week days on which insulin coma therapy was administered, a moderate increase in urinary corticosteroid excretion was consistently observed. On Saturdays and Sundays, when insulin was not given, urinary corticosteroid levels decreased. The 17-ketosteroid excretion did not parallel the corticosteroid excretion. Insulin coma therapy did not alter adrenocortical responsiveness to intravenous ACTH. Following the completion of insulin coma therapy, both urinary corticosteroid and 17-ketosteroid excretions remained at lower levels than during the pre-insulin control period. This observation suggests that basal adrenocortical function may be depressed by a course of insulin coma therapy.

Martin, William J.; Spittel, John A., Jr.; McConahey, William M.; Bennett, Warren A. (Mayo Clin. and Mayo Found., Rochester, Minn.): DIABETES MELLITUS COMPLICATED BY BACTEREMIA CAUSED BY GRAM-NEGATIVE BACILLI. A. M. A. Arch. Int. Med. *100*:214-20, August 1957.

Of 137 patients with bacteremia caused by gram-negative bacilli studied at the Mayo Clinic, fourteen had diabetes. The coli-aerogenes group of organisms accounted for twelve of these fourteen infections of the blood stream, while Proteus organisms were responsible in the other two instances. The urinary tract was the apparent portal of entry of the organisms in thirteen of the fourteen patients. Two of the fourteen patients died during treatment of the bacteremia as the result of serious renal disease, which probably made recovery virtually impossible. The recommended treatment for such infections is the use of a combination of a streptomycin compound and one of the tetracycline group of antibiotics. In an attempt to avoid the complication of such bacteremia in diabetic patients, vigorous treatment of infections of the urinary tract and antibiotic prophylaxis during operations on the urinary tract are urged for all diabetics.

Middleton, J. E.; and Griffiths, W. J. (St. Thomas's Hosp., London): RAPID COLORIMETRIC MICRO-METHOD FOR ESTIMATING GLUCOSE IN BLOOD AND C.S.F. USING GLUCOSE OXIDASE. Brit. M. J. *2*:1525-27, Dec. 28, 1957.

The authors describe a rapid and accurate colorimetric micromethod for the estimation of glucose in blood and cerebrospinal fluid in which no heat is required. The procedure utilizes a suitably buffered solution of glucose oxidase, peroxidase, and o-tolidine of *p*H 5. The normal fasting blood glucose is found to be from 50 to 90 mg. per 100 ml., which after oral glucose rises to a maximum of approximately 160 mg. per 100 ml. in normal subjects.

Miller, Emery C. (Dept. of Med., Bowman Gray Sch. of Med., Wake Forest Coll., Winston-Salem, N. C.): ORAL THERAPY OF DIABETES MELLITUS: TOLBUTAMIDE. North Carolina M. J. *18*:449-53, October 1957.

A nontoxic, oral drug that will adequately control the total diabetic metabolic disorder in all diabetic patients is not now and may never be known. The sulfonylureas are only an exploratory, tentative step toward such an agent. If used wisely in carefully selected patients, the sulfonylureas make possible successful oral treatment of diabetes mellitus. This encouraging development merits continuing intensive clinical and experimental study.

Miller, R. D. (Beverly, England): ENZYME TESTS FOR GLUCOSE. Lancet *1*:106-07, Jan. 11, 1958.

The author reports his experience with 932 samples of urine, each of which was tested by the Clinistix method and also by the standard Benedict technic. Of the 932 samples, twelve gave a false positive reaction. There were no false negatives. The author assumes that since all positive reactions to Clinistix must be confirmed by the Benedict technic, the problem of a false positive reaction is not significant. He concludes that the Clinistix method is a reliable test for glucose in the urine.

Möllerström, J.; and Sollberger, A. (Wenner-Gren Inst., Swedish Diabetic Found. and Caroline Inst., Stockholm, Sweden): THE 24-HOUR RHYTHM OF METABOLIC PROCESSES IN DIABETES. I. CITRIC ACID IN THE URINE. Acta. med. scandinav. *160*:25-46, Jan. 31, 1958.

One hundred and five twenty-four-hour measurements of citric acid output in the urine of fifty diabetics were studied with respect to mean daily output, nondiurnal trends during observation days and the twenty-four-hour changes which oc-

cur independently of mean levels and nondiurnal trends. The authors conclude that the mean daily output in the urine is proportional to the amount of food administered and seems inversely correlated with the amount of ketone excreted. The long term nondiurnal trends are influenced by changes in food, insulin and body weight. The amplitude-level law operated in the citric acid twenty-four-hour rhythm. The ranges of variation and the mean levels during twenty-four hours are positively correlated. This applies also to the pyruvic acid, chloride and total phosphate outputs in the urine and the pyruvic acid concentration in the blood. The presence of short-term, high-frequency variations superimposed upon the twenty-four-hour cycle is observed. It is supposed to be an endogenous primary rhythm giving rise to our normal food ingestion rhythm, which demands food at about four-hour intervals throughout the day.

Nielsen, Robert L.; Swanson, Heidi E.; Tanner, Donald C.; Williams, Robert H.; and O'Connell, Maureen (Univ. of Washington, School of Med., Seattle, Wash.): EFFECTS ON BLOOD SUGAR OF A NEW POTENT HYPOGLYCEMIC COMPOUND. A.M.A. Arch. Int. Med. *101*:211-15, February 1958.

Phenethyldiguanide (PEDG) is a potent hypoglycemic agent in the guinea pig. Hypoglycemia is accompanied by a marked fall in hepatic glucose output; however, hypoglycemia can be produced in the eviscerated animal. The degradation of insulin I^{131} is inhibited by prior administration of PEDG, but it is not felt that this action is of significance in the production of hypoglycemia.

Oakley, Wilfrid (London, S.E. 5, England): HYPOGLYCEMIA AND THE MIND. Brit. M. J. *1*:279, Feb. 1, 1958.

The author comments on the symptomatology of spontaneous hypoglycemia. He has found good psychotherapy sometimes more effective than low carbohydrate diet or buffer meals in the correction of low blood sugar levels.

Planta, F. von (Pathological Inst., Univ. of Zürich, Switzerland): NON INSULIN-PRODUCING ISLAND CELL TUMOR OF THE PANCREAS WITH PEPTIC ULCER (ZOLLINGER ELLISON'S SYNDROME). Schweiz. med. Wchnschr. *87*:1272-74, Oct. 12, 1957.

Zollinger Ellison's syndrome is characterized by a non insulin-producing insulinoma of the pancreas, with increased gastric acidity, gastric hypersecretion and ulcer of the gastrointestinal tract. The island tumors are multiple or single; more than half of them are malignant. The ulcers are localized or in the duodenum or the proximal parts of the jejunum or more rarely in the stomach. (German)

Pote, William W. H., Jr. (Dept. of Internal Medicine, Coll. of Med. Evangelists, Sch. of Medicine, Los Angeles, California): THE TREATMENT OF DIABETES MELLITUS. California Med. *88*:123-26, February 1958.

The treatment of diabetes mellitus continues to challenge all physicians regardless of special interest. Although there have been many advances, treatment still primarily centers around education of the patient, particularly in regard to the proper balance of diet, insulin and exercise. The exact role of the new oral insulin substitutes is not yet fully established. With proper consideration of the fundamentals of treatment and team approach, there can be life added to the years and years to the lives of our increasing diabetic population.

Pryce, I. G. (Research Dept., Runwell Hosp., Wickford, Essex, England): GLUCOSE-TOLERANCE TESTS. Lancet *1*:645-46, March 22, 1958.

The author comments on mathematical treatment of the data obtained in the intravenous glucose tolerance test. Further comment is made with regard to this test in mild diabetes both before and after treatment with carbutamide. The mode of action of carbutamide is still uncertain, and it is difficult to accept data from oral glucose tolerance tests and the daily fluctuations in blood glucose as proof of the absence of small differences in glucose utilization; the apparent inconstancy of the "total" index may therefore reflect a real change in rate of utilization —an observation of some interest.

Reid, James; Macdougall, A. I., and Andrews, M. M. (Clinical Chemotherapeutic Res. Unit of the Med. Res. Council, Western Infirmary, Glasgow, Scotland): ASPIRIN AND DIABETES MELLITUS. Brit. Med. J. *2*:1071-74, Nov. 9, 1957.

Disappearance of glycosuria and the return of fasting blood sugar to normal in a young diabetic during aspirin treatment for acute rheumatism led to re-investigation of the effect of salicylate in diabetes mellitus. An intensive two-week course of aspirin abolished glycosuria and lowered the fasting blood sugar to normal or nearly normal in seven patients with mild to moderately severe diabetes. No decisive effect on glucose tolerance was obtained, though the blood sugar curves were always lower during aspirin administration than they were either before or after. Moderate ketonuria in two patients was reduced to normal with aspirin. Clinical improvement accompanied the biochemical changes induced by aspirin, and while serious toxic manifestations were not conspicuous tinnitus and deafness were annoying. The possible place of aspirin in the treatment of diabetes mellitus is discussed. (*Ed.:See editorial comment, page 324.*)

Richardson, J. C.; and Hill, F. M. (Dept. of Med., Univ. of Toronto, and Toronto Genl. Hosp., Toronto, Can.): NEUROLOGIC DIAGNOSIS OF PANCREATIC ISLET CELL ADENOMA WITH HYPERINSULINISM. Neurology 7:793-97, Nov. 1957.

It is difficult to formulate rigid rules and principles as to when the neurologist must investigate the possibility of hyperinsulinism. Episodic cerebral symptoms of various types must lead to this consideration. It is seldom a matter of simple epileptic attacks of focal or generalized nature, and certainly one need not do blood sugar studies in every case of epilepsy. The convulsive attacks of hypoglycemia tend to occur after preceding coma of minutes' or hours' duration. With more prolonged symptoms the recurrence of spells of coma or confusion may be replaced by epilepsy which is secondary to cortical pathology. Seizures of various focal types and generalized attacks may occur. Many of the repetitive cerebral symptoms are due to an arrest or depression of cerebral function, rather than to irritability with seizure discharge. Thus one encounters transient paresis, numbness, diplopia, slurring of speech and so on. Suspicion of hypoglycemia is strengthened by the timing of symptoms at certain periods of the day, such as the early morning or on awakening. Episodes of erratic confused behavior are common and may be difficult to distinguish from temporal lobe seizures.

Rossi, E.; Vassella, F.; Schwamm, H. A.; Hug, G.; and Gitzelmann, R. (Pediat. Clin., Zürich, Switzerland): GLUCAGON—PROBLEMS; THE GLUCAGON TOLERANCE TEST AND ITS CLINICAL SIGNIFICANCE. Schweiz. med. Wchnschr. *87*:1010-16, Aug. 3, 1957.

A clinical evaluation of the results of glucagon tolerance curves is presented. In a first series of tests, glucagon tolerance curves were determined in healthy children ranging in age from four months to thirteen years. In all children a definite rise in blood-sugar values was noted after ten and twenty minutes; the inorganic serum phosphate level fell after thirty minutes, and no change was noted in the pyruvic acid level. The peripheral utilization of glucose, measured and compared under various conditions, attained maximal values under the combined effect of insulin and glucagon. The conclusion is thus made that insulin and glucagon exhibit synergistic activity, which can be of great significance in future therapeutic application. The glucagon tolerance curve, carried out in forty-five youthful diabetics, allowed their classification into three principal groups: In group 1 the blood sugar level showed a normal rise and return to original values; group 2 showed a rise in blood sugar levels which, however, remained high, and group 3 showed an insufficient rise, followed by a severe fall in blood sugar levels below original levels. It was shown that after various periods of fasting, normal healthy volunteers can show glucagon tolerance curves which assume severe diabetic forms, depending upon the duration of the preceding fasting period. The glucagon tolerance curve enables a judgment as to the momentary severity of the diabetes, and gives important therapeutic indications. The conclusion is that in principle it serves no purpose to separate insulin from glucagon because both are essential for the flow of glucose throughout the body. The publications, which will appear in their original form in the *Helvetica Paediatrica Acta,* thus refute the concept of antagonistic action of insulin and glucagon.

Rudomin, Z. P. (Del Departamento de Neurofisiología de la Escuela Nacional de Ciencias Biologicas, Mexico): CONDITIONAL GLYCOSURIA: NERVOUS SYSTEM CONTROL OF THE TUBULAR REABSORPTION OF GLUCOSE. Acta physiol. latinoam. 7:124-40, 1957.

An experimental approach to the problem of the role of central nervous system in the control of renal tubular function is presented.

Glycosuria induced by intravenous injection of adrenaline (100 μg. per kg. of body weight) was associated with the sound of a ring bell. After several of these coincidences, the sound of the bell was able to produce the glycosuria without hyperglycemia or polyuria. Conditioned glycosuria was as great in magnitude or duration as the one obtained by adrenaline injection. It is concluded that the central nervous system inhibits the tubular reabsorption of glucose, and that this brings the appearance of sugar in the urine. With the idea of looking into the mechanism of this reflex effect, one of the kidneys was denervated in an animal with well-established conditioned glycosuria. As denervation produced the disappearance of that conditioned reflex for that particular kidney, it was concluded that reabsorption of glucose by renal tubules can be under the reflex control of the central nervous system and that nervous pathways constitute the efferent limbs of this reflex.

Runge, Thomas M.; Gilbert, Joseph T.; Pelphrey, Charles F.; and Gaddy, H. R. (Capital National Bank Bldg., Austin, Texas): INSULINOMA SIMULATING EPILEPSY. Neurology 7: 870-72, December 1957.

A case of hyperinsulinism simulating epilepsy is reported. The possibility of pheochromocytoma both clinically and from laboratory studies (Regitine test) is mentioned.

Russell, Jane A. (Dept. of Biochemistry, Emory University, Atlanta, Ga.): EFFECTS OF GROWTH HORMONE ON PROTEIN AND CARBOHYDRATE METABOLISM. Am. J. Clin. Nutrition 5: 404-16, July-August 1957.

The author of this article rather expertly focuses some of the multitudinous and seemingly unrelated facts regarding the growth hormone on her immediate problem of trying to combine the *effects* of the growth hormone (and/or other closely related pituitary factors) with the *action* of the growth hormone on carbohydrate metabolism. More simply, this is trying to combine in theory at least the effects of the growth hormone on nitrogen metabolism with some of those on metabolism of the carbohydrate complex. She points out that there is reason to believe that the action of the growth hormone is one of conservation in body tissues with respect to nitrogen, particularly when the supply of exogenous protein is restricted. She then points out the similarity to carbohydrate where, in the fasting animal under specific circumstances which she detailed, there is a marked increase in cardiac muscle glycogen with administration of exogenous growth hormone. She then attempts to prove with necessarily uncritical information that the fasting state of the animal must affect the rate of secretion of growth hormone rather than its activity per se. A side issue of her discussion is that growth hormone may be the important pituitary hormone in relation to carbohydrate metabolism rather than a separate one or number of pituitary hormones such as the so-called diabetogenic hormone, etc. Her main interest in formulating a hypothesis of growth hormone relationship to protein and carbohydrate metabolism may be to focus what is known about these subjects into a spotlight which is susceptible to experiment.

Saifer, Abraham, and Gerstenfeld, Shirley (Biochemistry Dept., Isaac Albert Res. Inst., Jewish Chronic Disease Hosp., Brooklyn, New York): THE PHOTOMETRIC MICRODETERMINATION OF BLOOD GLUCOSE WITH GLUCOSE OXIDASE. J. Lab. & Clin. Med. 51:448-60, March 1958.

The authors describe a simple, rapid, quantitative, spectro photometric method for the microdetermination of heparinized plasma or blood glucose using glucose oxidase, a specific enzyme for beta d-glucose. Attempts to apply the method directly to plasma (or serum) were unsuccessful because of the presence of variable amounts of inhibitory substances, e.g., uric acid and ascorbic acid. Since these are removed during preparation of Somogyi zinc filtrates, subsequent determinations were performed on such filtrates in comparison with the Nelson-Somogyi procedure. Comparative data (in mg. per cent) with the glucose oxidase (G.O.) and the Nelson-Somogyi (N.S.) methods were obtained from fasting plasma. Both the G.O. and N.S. methods have a ± 2 per cent error as determined by triplicate analyses on fifteen standard serum samples. For routine analyses, a rapid simplified procedure is described for use with a photoelectric colorimeter which employs syringe pipettes and a decantation step.

Schamaun, M.; Deucher, F.; and Gablinger, S. (Dept. of Surg. and Dept. of Med., University of Zürich, Switzerland): SPONTANEOUS HYPOGLYCEMIA DUE TO A LARGE SUPRARENAL CORTICAL TUMOR; CURE BY SURGICAL REMOVAL. Schweiz. med. Wchnschr. 87:1348-52, Nov. 2, 1957.

Spells of hypoglycemia with complete loss of consciousness in a thirty-seven-year-old man led to surgical exploration. This revealed a large tumor of the right suprarenal gland with compression of the inferior vena cava and of the portal

vein. The tumor weighed 1.7 kg. and appeared histologically as an adenoma of the adrenal cortex. Removal of the tumor together with the right kidney led to disappearance of hypoglycemia. Six months after operation the patient was in good condition. Review of the respective literature. (German)

Schauble, Muriel K.; and Baker, Roger Denio (Durham, N. C.): THE INFLAMMATORY RESPONSE IN ACUTE ALLOXAN DIABETES. ENHANCED PROLIFERATION OF RHIZOPUS AND MICROCOCCUS IN CUTANEOUS LESIONS OF RABBITS. A.M.A. Arch. Path. *64*:563-69, November 1957.

In order to study the inflammatory response, suspensions of Micrococcus pyogenes var. aureus and spores of Rhizopus oryzae were injected intracutaneously into three groups of rabbits: (1) those in the acute toxic phase of alloxan diabetes, (2) those in the chronic phase of alloxan diabetes, and (3) normal controls. There was a notable polymorphonuclear response to both the Micrococcus and the Rhizopus in the acute toxic alloxan-treated as well as in the normal control and chronically diabetic rabbits. There was greater proliferation of both Micrococcus and Rhizopus in cutaneous lesions in acutely toxic alloxan-diabetic than in the normal or chronic diabetic rabbits. The increase in proliferation was accompanied in the Rhizopus lesions by vascular invasion by the organism. This is a characteristic finding in human cases and experimental lesions where the fungus is actively proliferating. Greater nuclear fragmentation of the polymorphonuclear cells was noted in the lesions of rabbits in the acute toxic stage of alloxan diabetes. It was impossible to determine whether this increased fragmentation was caused by increased proliferation of the infecting agents. It is concluded that there is a notable inflammatory response to both Micrococcus and Rhizopus in experimental alloxan diabetes and that the increased susceptibility to those organisms in the acute diabetic state is not due to a failure of migration of polymorphonuclear cells to the site of infection but to some other factor.

Spratt, Irving L., and Hardin, Robert C. (Dept. of Internal Medicine, State Univ. of Iowa Coll. of Med., Iowa City, Ia.): THE HISTORY OF TREATED DIABETES MELLITUS: A CONTRAST OF THE YOUNG AND THE OLD. J. Iowa M. Soc. *47*: 571-76, September 1957.

The problems of diabetes to be faced today are quite complex, the authors observe. The patients are of all ages, but most are elderly and have disease of relatively short duration. In a lesser number, the onset of diabetes has been early in life, and for the first ten years no clinically serious complications occur. Later, capillary degeneration may appear, and its chief manifestation is retinopathy. Contrastingly, the older patients have as their most frequent complication arteriosclerosis affecting the legs and the heart. This is greater both in incidence and in severity than among persons of equal age without diabetes. Infections, particularly of the respiratory system and urinary tract, are common in older diabetics. Diagnosis of diabetes is usually easy in the young because the symptoms are severe. The older patient more often has mild diabetes, but this fact seems to bear little relation to the severity of complications. In fact, from the clinical point of view, the complication may precede diabetes, and the physician must be ever alert to this possibility. The older patient poses no great problem in control of diabetes, for it is usually mild. But he requires maximum attention for his complications.

Stadie, William C. (Emeritus Professor, Research Medicine, University of Pennsylvania Sch. of Med., Philadelphia, Pa.): NEWER CONCEPTS OF THE ACTION OF INSULIN. Am. J. Clin. Nutrition *5*:393-403, July-August 1957.

This is a very provocative article both for the clinician and for the researcher. Dr. Stadie starts his discussion by explaining the so-called transport hypothesis of the action of insulin and points out that this theory cannot be generalized to apply to all other types of tissue. The discussion is pinpointed in the first portion to his explanation of two distinct metabolic derangements in the diabetic liver, (1) pertaining to glucose metabolism, and (2) pertaining to fatty acid synthesis. He points out that in the normal liver slice in vitro the effects of insulin upon fatty acid synthesis from lactate, acetate or from pyruvate are easily demonstrable. A reversal toward normal of these metabolic defects in the diabetic liver slices cannot be demonstrated. However, the response to insulin in muscle from normal and diabetic rats is immediate. This certainly points out a fundamental difference in the mechanism of insulin reaction in at least two types of tissue. He cites further experimental evidence that there are two pathways of fatty acid metabolism, only one of which is impaired in the diabetic. These two pathways are those of oxidation and synthesis and are clearly diagrammed by the author's own schema. He then brings together several different theories to form a whole concept (or at least a partial one) including theories indicating that oxidative phosphorylation is impaired in the diabetic status and may be responsible for both fat and carbohydrate metabolism aberrations; the theory of chemical binding of insulin by muscle and other tissues and most recently the phenomenon which might be called "metabolic adaptation" brought about by insulin. "Adaptation" is a change in the function of enzymatic systems of tissues in the presence of insulin which requires considerable time for full development. Lastly, he presents what he calls a unified concept of insulin action in muscle, liver, and adipose tissue which he does not claim is a complete concept or necessarily completely accurate but which certainly supplies provocation both clinically and researchwise.

Sterzing, Ludwig (Dept. of Med., Municipal Hosp., Heilbronn, Germany): A CASE OF GENERALIZED EPIDERMOLYTIC REACTION WITH SECONDARY PEMPHIGUS DUE TO THE ADMINISTRATION OF BZ-55 FOR DIABETES MELLITUS. Deutsche med. Wchnschr. *83*:100-02, Jan. 17, 1958.

A fifty-eight-year-old female with known diabetes of about seven years' duration and a daily insulin requirement of 44 units was transferred to BZ-55. Four grams were given on the first day, 3.5 gm. on the second and third. The dose was then decreased daily by 0.5 gm. The patient's diabetes was well controlled without additional insulin from the fourth day on. However, she had developed nausea and vomiting since the third day, followed by fever one week later. Since eosinophilia of 7 per cent was found, carbutamide was replaced by tolbutamide. Nevertheless, the fever persisted and pruritus with severe skin and mucous membrane swelling occurred on the fifteenth day of treatment. Despite discontinuation of the oral antidiabetics and reinstitution of insulin treatment the patient developed severely toxic generalized symptoms with pemphigus-like eruptions on skin and particularly the mucous membranes: conjunctiva, mouth, tongue and glottis. Calcium injections and antihistaminics did not give relief. Gradual improvement was obtained with steroid treatment (ACTH and

prednisolone). Free sulfonamide was discovered in the serum as long as twenty-five days after discontinuation of carbutamide. The patient recovered slowly; large areas of skin pigmentation persisted and the conjunctivitis led to small abscesses of the lids resulting in bilateral entropium.

Stowers, J. M.; Mahler, R. F.; and Hunter, R. B. (Dept. of Med., Pharmacol. & Therapeutics, Univ. of St. Andrews, Queens Coll., Dundee, Scotland): PHARMACOLOGY AND MODE OF ACTION OF THE SULPHONYLUREAS IN MAN. Lancet *1*: 278-83, Feb. 8, 1958.

After reviewing the literature, the authors conclude that the sulfonylureas significantly reduce the output of glucose from the liver in both labile and stable diabetics; also, they decrease the variation in the blood sugar of most of the unstable cases. No evidence of increased insulin secretion was found.

Thomas, Constance P. F. (Chigwell, Essex, England): HYPOGLYCAEMIA AND THE MIND. Brit. M. J. *1*:643, Mar. 15, 1958.

The author disagrees with a suggested treatment of hypoglycemia that appeared in a previous issue of the journal (Feb. 8, 1958, p. 341). A dietary intake normal in carbohydrate is favored as opposed to a low carbohydrate intake.

Törnblom, Nils (Med. Clin. and the Central Lab., University Hosp., Upsala, Sweden): MECHANICAL ISOLATION OF GLOMERULI FROM HUMAN KIDNEYS AND OF HYALINE SUBSTANCE FROM GLOMERULI WITH KIMMELSTIEL-WILSON CHANGES. Acta med. scandinav. *159*:369-73, Dec. 16, 1957.

The author describes methods of mechanically isolating glomeruli from human kidneys obtained at autopsy and of isolating hyaline substance from renal glomeruli with Kimmelstiel-Wilson changes.

Tulloch, J. A. (Dept. of Medicine, U.C.W.I., Jamaica): EXPERIENCE IN JAMAICA WITH THE ORAL TREATMENT OF DIABETES. West Indian Med. J. *6*:43-54, March 1957.

The findings herewith reported are in keeping with the observation that middle-aged nonobese diabetic subjects whose disease is relatively mild are likely to respond to carbutamide administration.

The toxic effects induced by the high dosage of carbutamide are of interest—transient albuminuria was noted in two cases, neutropenia in two, eosinophilia in two, relative thrombocytopenia in one, headache and giddiness in one and episodes of prolonged drowsiness and coma in one. These last effects were initially thought to be hypoglycemic in nature and responded to intravenous glucose, but the blood sugar levels were not low, e.g., 140 mg. per 100 ml. on one occasion. In addition, the drowsy state was prolonged for several hours on another occasion in spite of large dosage of glucose by mouth and intravenously. From the experience gained it must be concluded that carbutamide has little part to play in the treatment of hospitalized diabetic patients in Jamaica. In the dosage necessary to achieve adequate reduction in the blood sugar, toxic effects of one form or another are too common.

Van der Sar, A.; Bosschieter, E.; Hugenholtz, M. J.; and Van der Hoeven, L. (Public Health Service, Curaçao, Netherlands Antilles): SPONTANEOUS HYPOGLYCAEMIC ATTACKS DUE TO AN INSULINOMA IN A DIABETIC: REPORT ON A CASE. Docum. med. geog. et trop. *8*:85-95, March 1956.

This article reports the case history of a forty-six-year-old diabetic female who was treated with diet and 40 units insulin per day from 1940 to 1946, at which time insulin was discontinued since the diabetes seemed to have improved. Since 1948 the patient experienced frequent attacks of sweating, trembling, confusion and muscular cramps. These attacks occurred mainly in the morning and increased gradually in frequency and severity. In 1952 the patient was admitted to the hospital in diabetic coma and responded to emergency treatment of large doses of regular insulin. Three days after discontinuation of insulin, patient lapsed again into a state of unconsciousness with cramps and perspiration. She responded to glucose administration. An oral glucose tolerance test showed a low fasting blood sugar level but a diabetic curve. Hypoglycemic attacks could be precipitated by fasting and responded to ACTH and cortisone administration. Liver function tests were normal. The patient was explored and a small tumor was found in the head of the pancreas. The tumor was removed and examined histologically. It was encapsulated in fibrous tissue and contained exocrine as well as islet cells. Its hormonal content and activity, however, were not determined. After recovery from the operation the patient's diabetes became manifest again and required insulin. The patient became mentally disturbed.

Venkatesan, T. V. (Madurai, India): THE NEW ORAL ANTIDIABETIC DRUGS. Med. Digest *25*:22, January 1957.

The results of various workers show that BZ-55 (carbutamide) is not a substitute for insulin, the author says. It has a place only in the treatment of the middle-aged, obese diabetic. Dietetic control remains the mainstay of treatment.

Wall, J. S.; Steele, R.; de Bodo, R. C.; and Altszuler, N. (New York Univ. Coll. Med., New York, and Brookhaven Natl. Lab., Upton, L. I., N. Y.): EFFECT OF INSULIN ON UTILIZATION AND PRODUCTION OF CIRCULATING GLUCOSE. Am. J. Physiol. *189*:43-50, April 1957.

C_{14} glucose was administered continuously to unanesthetized normal dogs by intravenous infusion following a priming dose at a rate that maintained the specific activity of the circulating glucose at a nearly constant level. Glucagon-free insulin was then administered intravenously in varying doses. Samples of blood were collected at intervals throughout the experiment and more frequently just subsequent to insulin injection. The glucose concentration of the circulating blood and the specific activity of this glucose, when considered together, allow calculations to be made of (a) the outflow of glucose toward the tissue cells, and (b) the inflow of glucose from the liver during the period after insulin injection. By this means it was shown that increased glucose uptake by the tissues is much more important than decreased delivery of glucose by the liver in bringing about insulin-induced hypoglycemia. It was also shown that recovery from hypoglycemia is brought about by increased glucose delivery by the liver and not by a decrease in tissue uptake of glucose below the pre-insulin level. Alternative methods of calculation of absolute values for glucose inflow and outflow during periods of changing blood glucose concentrations were discussed and evaluated.

Wall, J. S.; Steele, R.; DeBodo, R. C.; and Altszuler, N. (Dept. of Pharmacology, New York University Coll. of Medicine, New York City, and the Dept. of Biology, Brookhaven National Lab., Upton. New York): MECHANISM OF INSULIN HYPERSENSITIVITY IN THE HYPOPHYSECTOMIZED DOG. Am. J. Physiol. *189*:51-56, April 1957.

Following the intravenous injection of glucagon-free insulin into unanesthetized hypophysectomized dogs in the postabsorptive state, changes in the rates of glucose outflow from the plas-

ma into the tissues and glucose inflow into the plasma from the liver were determined. By the use of C^{14} glucose, these flow rates were determined simultaneously while the plasma glucose concentration was changing. In the hypophysectomized dog, the same amount of insulin caused a greater increase in outflow from the plasma than in the normal dog; the duration of the period of increased outflow was not significantly longer. The liver of the hypophysectomized dog failed to release enough glucose in response to the induced hypoglycemia to restore the plasma glucose concentration promptly to the pre-insulin level, whereas the liver of the normal dog responded readily. Because of the greater outflow of plasma glucose and inadequate inflow of glucose and the lower initial plasma glucose concentration, insulin causes a more severe and prolonged hypoglycemia in the hypophysectomized animal. The insulin hypersensitivity of the hypophysectomized dog may thus be attributed to two separate and perhaps equally important factors: (a) A small amount of injected insulin results in a greater increase in the rate of plasma glucose uptake by the tissues than in the normal animal; and (b) the hypoglycemia in the hypophysectomized dog is less effective in bringing about the release of sufficient amounts of glucose by the liver than in the normal one.

Weaver, J. A.; Prout, T. E.; Scott, G. W.; and Asper, S. P. (Dept. Med., Johns Hopkins Univ. Sch. Med. & Johns Hopkins Hosp., Baltimore, Md.): ROLE OF INSULIN IN ACUTE HYPOGLYCAEMIC ACTION OF TOLBUTAMIDE. Brit. M. J. *1*:425-29, Feb. 22, 1958.

The authors treated ten patients with diabetes mellitus of recent onset, not controlled by diet or previously treated with insulin, with a single dose of 3 gm. of tolbutamide orally. Eight of these ten patients showed a significant fall in the venous glucose concentration. Studies on the difference between the arterial (A) and venous (V) glucose concentrations, expressed as A-V/A, have shown no evidence of an increase in the uptake of glucose by the peripheral tissues in patients given tolbutamide. Studies of insulin-like activity of serum, as assayed by the rat hemidiaphragm method, have shown that there is no change in the insulin-like activity in the patients' serum before and after tolbutamide administration. The rate of disappearance of intravenously administered insulin I^{131} from plasma was studied in normal rabbits by the electrophoretic technic. No difference in the rate of disappearance of insulin I^{131} was found following the injection intravenously of tolbutamide as compared with untreated animals. These studies support the view that the hypoglycemic action of tolbutamide is not produced by increasing the effective level of insulin.

Wells, Ronald, and Yam, Tan Bock (Singapore): ORAL THERAPY FOR DIABETICS WITH TUBERCULOSIS. Brit. M. J. *1*:220, Jan. 25, 1958.

The authors report their experiences with tolbutamide therapy in over 300 diabetics, including thirty-four with active pulmonary tuberculosis. It was found that twenty of the thirty-four tuberculous diabetics were well controlled on tolbutamide therapy and that six more were fairly well controlled. The remaining eight patients in this group were poorly controlled on tolbutamide and were eventually treated with insulin. In twenty-seven of these tuberculous diabetics who had previously been treated with insulin, it was found that their control on tolbutamide was at least as good in twenty patients and was actually better in seven cases. This study was initiated partially because the authors found it virtually impossible to resist the insistent demand for the "new tablets" from diabetics of all types.

Wenger, Verena (Med. Policlin., Zürich, Switzerland): MODE OF ACTION OF ORAL ANTIDIABETIC DRUGS: SULFONYLUREA AND PITUITARY-CORTICOADRENAL-SYSTEM. Helvet. med. acta *24*:91-99, July 1957.

In diabetics, sulfonylurea has no influence on the excretion of urinary steroids. It does not impede the responsiveness of the adrenal cortex to ACTH, or suppress the carbohydrate effect of exogenous cortisol. The point of action of the sulfonylureas is not to be sought in the pituitary-adrenal system but in some other part of carbohydrate metabolic regulation, the author states.

Williams, Roger D.; and Ellison, Edwin H. (Dept. of Surgery, Ohio State Univ. Health Center, Columbus, Ohio): DIAGNOSIS AND SURGICAL MANAGEMENT OF HYPERINSULINISM. A.M.A. Arch. Surg. 75:584-89, October 1957.

The surgeon is primarily concerned with islet-cell adenomas. Alimentary and functional hypoglycemias require dietary management, and hormonal therapy is indicated in the treament of hypoglycemia due to endocrine deficiency. Islet-cell hyperplasia should not be considered the cause of hyperinsulinism in the adult. Insulomas may occur anywhere in the pancreas and are occasionally reported in the site of ectopic pancreatic tissue. Three out of four, however, will be found in the body and tail of the pancreas. Furthermore, in about one out of six reported cases more than one tumor was found. Unfortunately, approximately 10 per cent of islet-cell adenomas are malignant and metastasize to the liver and regional lymph nodes. Half of these tumors are also capable of insulin production.

Wise, George N. DIABETIC RETINOPATHY. A.M.A. Arch. Ophth. 59:303, February 1958.

Evidence was presented to show that neither the lipid droplets in the endothelial cells, as described by Ballentyne, nor the retinal micro-aneurysm constitutes the initial lesion in diabetic retinopathy. Data indicating that the primary vascular lesion in diabetes may well be due to some derangement in the mucopolysaccharide metabolism were shown. An even closer relationship between the retinal micro-aneurysm and the diabetic exudate than that described by Ballentyne probably holds. Evidence was presented to indicate that all diabetic exudates occur in arc or ring form about clusters or groups of retinal micro-aneurysms, whether clinically visible or not. Evidence was presented to challenge the strongly held medical view that the major vascular complications of diabetes are primarily arterial in nature.

ORGANIZATION SECTION

OFFICERS AND MEMBERS OF COUNCIL, AMERICAN DIABETES ASSOCIATION, 1958-1959

HONORARY PRESIDENT, ELLIOTT P. JOSLIN, M.D., *Boston*

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MEMBERS OF COUNCIL

TERM EXPIRING 1959

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W. WALLACE DYER, M.D., *Philadelphia*
EDWIN W. GATES, M.D., *Niagara Falls*
HARVEY C. KNOWLES, JR., M.D., *Cincinnati*
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TERM EXPIRING 1960

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TERM EXPIRING 1961

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LAURANCE W. KINSELL, M.D., *Oakland*
RACHMIEL LEVINE, M.D., *Chicago*
KELLY M. WEST, M.D., *Oklahoma City*

PAST PRESIDENTS

HENRY T. RICKETTS, M.D., *Chicago;*
FREDERICK W. WILLIAMS, M.D., *New York;* JOHN A. REED, M.D., *Washington, D.C.*

ELECT NEW OFFICERS AND COUNCILORS FOR 1958-59

The Eighteenth Annual Meeting of the American Diabetes Association was held in San Francisco, June 21-22, 1958. At the Business Session on June 22, Alexander Marble, M.D., Boston, was elected President for this organizational year to succeed John A. Reed, M.D., Washington, D.C. Francis D. W. Lukens, M.D., Philadelphia, was elected First Vice President; Franklin B. Peck, Sr., M.D., Indianapolis, Second Vice President; E. Paul Sheridan, M.D., Denver, Secretary; and Thomas P. Sharkey, M.D., Dayton, Treasurer. Drs. Marble, Lukens and Peck served in 1957-58 as First Vice President, Second Vice President and Secretary respectively. All the officers will serve through the Nineteenth Annual Meeting of the Association, which will be held in Atlantic City, New Jersey, June 6-7, 1959.

At this Business Session, Joseph T. Beardwood, Jr., M.D., Philadelphia; Arthur R. Colwell, Sr., M.D., Chicago; Joseph H. Crampton, M.D., Seattle; Laurance W. Kinsell, M.D., Oakland; Rachmiel Levine, M.D., Chicago; and Kelly M. West, M.D., Oklahoma City, were elected to the Council for the three-year term expiring in 1961. Laurentius O. Underdahl, M.D., Rochester, Minnesota, was elected to fill the unexpired term ending in 1959 of E. Paul Sheridan, M.D., newly elected Secretary.

POSTGRADUATE COURSE SERIES

The SEVENTH POSTGRADUATE COURSE IN DIABETES AND BASIC METABOLIC PROBLEMS will be held by the American Diabetes Association on Jan. 21, 22 and 23, 1959, in St. Louis, Missouri. William H. Olmsted, M.D., of St. Louis, will be Director, with Henry E. Oppenheimer, M.D., St. Louis, Co-Director. Developed by the Association's Committee on Professional Education, the Postgraduate Course series is open to members of the medical profession. Registration fee will be $50 for members and $100 for nonmembers. All inquiries and applications should be addressed to the National Office of the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

The tentative program of the Course includes these major half-day subjects: "The Pathophysiology of Insulin," "The Treatment of Diabetes: General Principles," "Relationship of Lipid Metabolism to Diabetes," "Special Problems in the Management of Diabetes," "Complications of Diabetes," and "The Oral Hypoglycemic Agents." Round-table conferences, a new feature in our Postgraduate Course Series, will be held on January 22 at the close of the afternoon session. Registrants will be divided into groups of sixteen or less, so that questions may be addressed to members of the faculty. The session leader may direct these discussions into any area he wishes, including subjects already presented or scheduled for presentation.

The SIXTH POSTGRADUATE COURSE IN DIABETES AND BASIC METABOLIC PROBLEMS offered by the American Diabetes Association was held in Atlanta, Georgia, on Jan. 22, 23 and 24, 1958. The Course, well received by those who attended, was developed by the Committee on Professional Education of the American Diabetes Association. Christopher J. McLoughlin, M.D., Atlanta, was Director, with C. Raymond Arp, M.D., Atlanta, and Walter L. Bloom, M.D., Atlanta, as Associate Directors.

A registration breakdown for the Sixth Postgraduate Course, and a comparison with the five previous Courses, follows.

REGISTRANTS	1958 Atlanta	1957 Columbus	1956 Dallas	1955 Philadelphia	1954 Rochester	1953 Toronto
Members	78	83	82	135	83	93
Membership pending	47	55	52	23	24	23
Nonmembers	53	57	47	18	17	61
TOTAL	178	195	181	176	124	177
OTHERS ATTENDING						
Part-time registrants	1	1		2		
*Graduate students				1	†	†
*Fellows	1		2	3	†	†
*Residents	14	16	10	10	†	†
*Interns	4	8	4	5	†	†
*Medical students	2	13	61	11	†	†
*Others		25				
Councilors and Faculty	40	34	48	41	35	35
Guests	6	12	4	6		2
TOTAL	68	109	129	79	35	37
TOTAL OF ALL CATEGORIES	246	304	310	255	159	214
ADDITIONAL DATA						
Cancellations	19	12	12	15	25	5
Applications rejected due to limited facilities					47	92
Attendance at Banquet	245	200	324	246	208	236

*From metropolitan area of Course location.
†Graduate Students, Fellows, Residents, Interns and Medical Students were not formally registered in 1954 and 1953.

1959 LILLY AWARD

The third annual Lilly Award will be given at the Nineteenth Annual Meeting, June 6-7, 1959, in Atlantic City, New Jersey. The following stipulations govern the contest for the award, which is supported by Eli Lilly and Company and consists of $1,000 and a medal.

Purpose: To recognize demonstrated research in the field of diabetes, taking into consideration independence of thought and originality.

Eligibility: Any investigator in an appropriate field of work closely related to diabetes who is less than forty years of age on January 1 of the year in which the award is made. The research will not necessarily be judged in comparison to the work of more mature and experienced workers. The candidate should be a resident of the United States or Canada.

Nominations: Nominations for the award will be solicited from the members of the American Diabetes Association. Such nominations will be requested by repeated notices to be published in DIABETES. Names of nominees will be sent to the Chairman of the Committee on Scientific Awards and must be received before January 1 of the year of the award. The nomination should be accompanied by full information concerning the nominee's personality, training and research work. Six copies of each item should be submitted. No member may send in more than one nomination. A list of the nominee's publications, if any, and six copies of the publication or manuscript for which the award is to be given should also accompany the nomination. At the discretion of the Committee on Scientific Awards, the award may be given for work published during the year prior to January 1 of the same year of the award. The nominee should be actively engaged at that time in the line of research for which the award is to be made.

Announcement: The name of the winner will be announced in the program of the Annual Meeting of the Association, and the award presented at that meeting. The winner, subject to the approval of the Committee on Scientific Programs, will be invited to present a paper on the subject of his work. Papers considered for the award must be submitted with the idea that they will be published in whole or in part in DIABETES if found acceptable to the Editor and/or Editorial Board. If the Committee should decide that no outstanding work has been presented for this consideration, the award will not be made.

Award: In addition to the monetary award and the medal, traveling expenses will be given to make it possible for the recipient to receive his award in person at the Annual Meeting.

ADA RESEARCH FELLOWSHIP

At least one Fellowship for the academic year 1959-60 will be awarded by The Committee on Research and Fellowships of the American Diabetes Association. Deadline for applications is Nov. 15, 1958. Requests for application forms and inquiries should be addressed to Mr. J. Richard Connelly, Executive Director, who will forward the information to the Committee.

DIABETES WEEK, 1958

The week of November 16-22 will be observed as Diabetes Week. Affiliate Associations and Committees on Detection of County and State Medical Societies are urged to note these dates in making plans for development of Public Education and Detection programs. Traditionally, the week which precedes Thanksgiving is the official Diabetes Week.

ADA FORECAST INCLUDES SUMMER CAMP LIST

An up-to-date list of summer camps for diabetic children, containing detailed information about each camp, was published in the May-June 1958 issue of the ADA FORECAST. A map showing geographic locations was also included. Members of the American Diabetes Association and readers of the Journal may obtain free single copies of a reprint of the article on request.

DIABETES ABSTRACTS

The Volume 5, Number 4 (October 1946) issue of DIABETES ABSTRACTS, which contains the five-year cumulative index for Volumes 1-5, is available without charge upon request to the American Diabetes Association, Inc., 1 East 45th St., New York 17, N. Y.

NEW MEMBERS

Active

The following were elected as of June 1, 1958, and July 1, 1958:

Alabama

Cleveland, Hunt	Anniston
Meyer, Isidore S.	Decatur
Miller, William L.	Gadsden
Ward, William Q.	Russellville
Williams, Jonathan R.	Selma

California

Johnson, Ben B.	San Francisco

Colorado

Jenkins, Dalton	Denver

Georgia

Beasley, E. W., Jr.	Atlanta

Illinois

Lambert, James H.	Joliet

Indiana

Brown, Wendell E.	Indianapolis

Michigan

Caputo, Nancy T.	Detroit
Hallen, Leonard J.	Detroit

New York

Blatt, Kurt B.	Haverstraw
Gittinger, W. C.	Brooklyn
Mann, Jay David	Albany

Ohio

Hoffman, Richard A.	Cincinnati

Oregon

Hare, Robert L.	Portland

Pennsylvania

McDonough, Gerard F.	Lock Haven

Tennessee

Smith, William Randolph	Cleveland

Other Countries

Argentina

Garzon-Maceda, F. G.	Cordoba

Brazil

Riet-Correa, Pery	Porto Alegre

Canada

Belmonte, Mimi M.	Montreal
Harpur, Eleanor R.	Pointe Claire
Nace, Paul F.	Hamilton

Associate

Florida

Kubus, Leana	St. Petersburg

NEWS OF AFFILIATE ASSOCIATIONS

The CONNECTICUT DIABETES ASSOCIATION held its Annual Meeting May 1 in Stratford, Connecticut. Seymour H. Rinzler, M.D., cardiologist associated with The Coronary Project of the Bureau of Nutrition of the City of New York, spoke on "The Relationship of Fats, Cholesterol and Coronary Heart Disease." New officers were elected, as follows: William Shepard, M.D., President; M. David Deren, M.D., Vice-President; and James C. Hart, M.D., Secretary-Treasurer. Council members who will serve two years are: Philip K. Bondy, M.D., Samuel Donner, M.D., William E. Hill, Sr., M.D., William G. Leeds, M.D., George S. Watson, M.D., Robert M. White, M.D., Leonard A. Howard, M.D., and Howard J. Lockward, M.D.

The NEW ENGLAND DIABETES ASSOCIATION conducted its Annual Dinner Meeting on June 5 at Cambridge, Massachusetts. An informal panel discussion on "Practical Aspects of the Management of Diabetic Outpatients" featured Alexander Marble, M.D., Samuel B. Beaser, M.D., David Hurwitz, M.D., and Rosemary Murphy, M.D. Arnold Relman, M.D., Chairman of the Program Committee, served as moderator.

The New England Diabetes Association and the Providence Medical Association convened in joint meeting February 4. Samuel B. Beaser, M.D., Chief of the Diabetes Clinic of the Beth Israel Hospital, discussed "Oral Hypoglycemic Agents," and Luke Gillespie, M.D., of the Harvard Medical School Department of Gynecology and Obstetrics, discussed "Management of Pregnancy in Diabetes." Louis I. Kramer, M.D., was moderator.

The NEW JERSEY DIABETES ASSOCIATION (Clinical Society) held its Annual Meeting on May 14 in East Orange. The program consisted of original papers presented by Society members.

The NEW YORK DIABETES ASSOCIATION (Clinical Society) met May 27 in the New York Academy of Medicine Building, New York City. The program included "Preliminary Clinical Observations on the Use of N^1-B-Phenethylformamidinyliminourea (DBI) as an Oral Hypoglycemic Substance," by Charles Weller, M.D., and Alice Macaulay, M.D.; "Observations on the Use of DBI in Labile Diabetes Mellitus," by William S. Norton II, M.D., and Stanley Bergen, M.D., with a discussion opened by Julius Pomeranze, M.D. The Annual Meeting of the Membership also took place.

NEWS NOTES

FDA OPENS DETROIT OFFICE

The United States Food and Drug Administration will open a new district office and laboratory in Detroit next fall that will enable it to provide greater protection for both consumers and manufacturers throughout the country. The office will serve Michigan and northern parts of Ohio and Indiana, a territory with fifteen million population now handled by the FDA offices in Chicago and Cincinnati. Twenty-eight inspectors and twenty scientists will account for the majority of the staff of sixty-seven. The new office is the first district base to be established since 1934.

AMERICAN PUBLIC HEALTH ASSOCIATION MEETING

The Eighty-sixth Annual Meeting of the American Public Health Association will be held in St. Louis, October 27-31. Topics to be covered in the Scientific Sessions will include the epidemiology of ionizing radiation injury, problems of meeting world food needs, original research in mental health, a reappraisal of health education in the space age, and public health aspects of nonliving environmental contaminants, including radiation, atmospheric pollution and noise.

GERONTOLOGICAL SOCIETY TO MEET

The Eleventh Annual Scientific Meeting of the Gerontological Society will be held Nov. 6, 7 and 8, 1958, at the Bellevue Stratford Hotel in Philadelphia.

AMERICAN DIETETIC ASSOCIATION MEETING

The Forty-first Annual Meeting of the American Dietetic Association will take place in Philadelphia Oct. 21-24, 1958.

GEIGY COLLOQUIUM

The Geigy Colloquium on Carbohydrate Metabolism in Childhood was held June 2-7 in Bern, Switzerland, under the sponsorship of the International Pediatric Association. George M. Guest, M.D., Cincinnati, presented a paper, "Dihydroxyacetone Tolerance Test for Glycogen Storage Disease." Other members of the American Diabetes Association participating were: Piero P. Foa, M.D., Chicago; Rene A. R. Francois, M.D., Lyon; Henri Lestradet, M.D., Paris; and Albert E. Renold, M.D., Boston. Carl F. Cori, M.D., St. Louis, Nobel Prize winner who delivered the Banting Memorial Lecture of the American Diabetes Association in 1955, also took part in the program.

PERSONALS

BARNETT GREENHOUSE, M.D., New Haven, spoke at the Sixth Annual Interim Scientific Meeting of the Medical Students' Aid Society of the Phi Lambda Kappa Medical Fraternity in Miami Beach, Florida, April 13-20. The title of his paper was "DBI and Chlorpropamide—Newer Oral Antidiabetic Drugs."

JAMES C. HART, M.D., was a member of the Executive Committee of the Twenty-fourth New England Health Institute which was held June 18-20 at Storrs, Connecticut. Studies of diabetes comprised a part of "Epidemiology of Chronic Disease," presented on June 19.

OBITUARIES

THOMAS P. MURDOCK, M.D., Meriden, Connecticut, was born March 6, 1888, in Meriden, and died at the age of sixty-nine. A member of the American Diabetes Association since 1952, he served on the Medical Board of the Visitors Institute of Living in Hartford and was Emeritus Chief of the Medical Division of Meriden Hospital. Dr. Murdock was a consultant for the Bristol, Undercliff, Silver Hills Foundation, and a member of the Advisory Committee of the Gaylord Farm Sanatorium. A trustee of the American Medical Association and a member of its Judicial Council, Dr. Murdock was also Secretary and President of the Connecticut Medical Examining Board. He served as a First Lieutenant in the Medical Corps of the United States Army from 1918 to 1919.

SIGMUND B. PAWLEY, M.D., Wilmington, Delaware, died at the age of sixty-four. Dr. Pawley, a member of the American Diabetes Association since 1954, was Associate in Metabolism at Wilmington General Hospital where he was attending physician. He received his M.D. degree from Jefferson Medical College, Philadelphia, in 1917, served as a Captain in the U. S. Medical Corps during World War I and was in command of a field hospital in France.

MARY E. VAN VLEET, M.D., Milwaukee, Wisconsin, was born July 25, 1919, and died at the age of thirty-eight. Dr. Van Vleet received her M.D. degree from Northwestern University in 1949, and later served on the attending staff at Milwaukee Hospital, Columbia Hospital and Milwaukee County Hospital. She was Clinical Instructor in Medicine at Marquette University School of Medicine. A member of the American Diabetes Association since 1953, Dr. Van Vleet was also a member of the American Geriatric Association.

HERMAN J. WOLFF, M.D., St. Paul, Minnesota, died recently at the age of fifty-one. Dr. Wolff received his M.B., M.D., and Ph.D. (Internal Medicine) degrees from the University of Minnesota, served an internship at the University of Minnesota Hospital and a residency at the Mayo Foundation in Rochester. A member of the American Diabetes Association since 1948, he served at the University of Minnesota as Assistant Clinical Professor of Medicine, and was former head of Medical Service at Miller Hospital in St. Paul. Dr. Wolff was an Associate in the American College of Physicians.